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17 MAR 2017

[redacted]
CASPER
[redacted]

Ref: H201700336

Dear [redacted]

Response to your request for official information

Thank you for your request of 6 February 2017 under the Official Information Act 1982 (the Act) for

> "1. What was the outcome of the request that Coroners forward decisions where suicide victims were using antidepressants as recorded in Minutes of the 136th Meeting of the Medicines Adverse Reactions Committee – 11 December 2008?
> 2. How many suspected adverse reaction reports have CARM received from Coroners since 2000 and how many of these related to SSRIs and/or suicide deaths?
> 3. In submitting data for new drug approvals or approvals for new indications or populations, are sponsors required to provide all published safety and efficacy data? If not, is it possible for sponsors to provide a limited number of studies which show efficacy and withhold studies which do not show efficacy and /or identify safety issues?
> 4. Have Medsafe or MARC reviewed the study conducted by Professor Peter Gotzsche in 2016 which found a doubling of suicide and violence risk in young people and if not, why not?
> 5. Do Medsafe and MARC consider Professor Gotzsche and the Nordic Cochrane Centre have expertise in conducting meta analyses of data and if not, why not?
> 6. What action if any have Medsafe and MARC taken in response to the finding of the Suicide Mortality Review Committee that 50% of their sample of adult males and mental health service users who died from suicide had a current prescription for antidepressants. If no action has been taken, why not?
> 7. Did the Suicide Mortality Review Committee bring the above data to the attention of Medsafe or MARC?
> 8. Do Medsafe consider the data on the use of pharmaceutical drugs by those who died from suicide in the SuMRC sample a signal and if so, what action does Medsafe intend to take to investigate the causal relationship between these drugs and suicide deaths?
> 9. Does Medsafe consider that the provision of genotyping results which showed whether a person was a poor, intermediate, extensive or ultra-rapid metaboliser would be useful in conducting causality assessments for adverse reaction reports. Would, for example, the provision of a genotype for CYP4502D6 assist with identifying a biologically plausible mechanism for an individuals adverse reaction

to drugs that are substrates of this enzyme? If this information was provided by consumers or others would Medsafe use it in conducting causality assessments?"

The information relating to this request is itemised below, with copies of documents attached. Some of the information you requested is already in the public domain. I have provided links to where this information is located.

1. What was the outcome of the request that Coroners forward decisions where suicide victims were using antidepressants as recorded in Minutes of the 136th Meeting of the Medicines Adverse Reactions Committee – 11 December 2008?

At the 138th Medicines Adverse Reactions Committee (MARC) meeting held on 11 June 2009, the committee noted the Waikato Coroner agreed to forward his decisions on medicine-related cases to the MARC and the New Zealand Pharmacovigilance Centre (NZPhvC). A similar request was made to other Coroner's offices throughout the country.

At the 139th MARC Meeting held on 10 September 2009, the committee noted that the number of Coroner's reports received by the Centre for Adverse Reactions Monitoring (CARM) had increased.

In 2011, Medsafe contacted the Chief Coroner by telephone. The Chief Coroner agreed that findings from all medicine-related deaths, including suicide, will be forwarded to both Medsafe and the NZPhvC. The NZPhvC continues to receive reports from Coroners. Details from these reports are entered into the database and help CARM and Medsafe identify safety concerns with approved medicines.

2. How many suspected adverse reaction reports have CARM received from Coroners since 2000 and how many of these related to SSRIs and/or suicide deaths?

Please refer to the document enclosed titled 'Coroners Cases' prepared by the NZPhvC. Since 2000, CARM has received 43 case reports from Coroners. Of these, four relate to SSRIs, seven relate to suicide and two relate to SSRIs and suicide.

3. In submitting data for new drug approvals or approvals for new indications or populations, are sponsors required to provide all published safety and efficacy data? If not, is it possible for sponsors to provide a limited number of studies which show efficacy and withhold studies which do not show efficacy and /or identify safety issues?

Data requirements for obtaining approval for medicines are contained in *Part 2: Obtaining approval for new and changed medicines and related products* of the *Guideline on the Regulation of Therapeutic Products in New Zealand*. This guideline is publicly available on the Medsafe website: www.medsafe.govt.nz/regulatory/current-guidelines.asp.

Section 5.3 contains information on general data requirements for new medicine applications. The requirements for safety and efficacy data for medicines is based on whether a medicine is considered to be higher-, intermediate- or lower-risk. In addition, during Medsafe's evaluation of data submitted by sponsors, up to two requests for information can be used to clarify specific aspects of the application. This can include requests for the sponsor to provide more information to support the product's efficacy and/or safety.

Applications for new and extended indications of approved medicines require justification or supporting clinical data (as appropriate). These applications are generally treated in the same way as new medicine applications. Supporting clinical data is almost always required for new and extended indications of approved medicines. The main reason why clinical data may not be required is when a generic product is aligning their indications with the innovator product. In this situation, Medsafe would have already evaluated the clinical data before the new or extended indication for the innovator product was approved.

You may also find this webpage on Medsafe's evaluation and approval process helpful: www.medsafe.govt.nz/Consumers/Safety-of-Medicines/Medsafe-Evaluation-Process.asp.

4. Have Medsafe or MARC reviewed the study conducted by Professor Peter Gotzsche in 2016 which found a doubling of suicide and violence risk in young people and if not, why not?

Medsafe has not reviewed the study on suicidality and aggression during antidepressant treatment which Professor Peter Gøtzsche was involved in [1]. Medsafe is not currently actively reviewing the risk of suicide and/or aggression in children and adolescents. Medsafe has previously reviewed this issue and issued advice. Medsafe continues to monitor the safety of SSRIs and antidepressants as for all medicines to identify signals of a possible problem. A safety signal could be a previously unknown adverse reaction or a change in the frequency or severity of a known side effect. Since Medsafe issued advice on this topic no new information that would significantly change this advice has been identified.

Known adverse reactions and their frequencies are included in medicine data sheets. Medicine data sheets are publicly available on the Medsafe website: www.medsafe.govt.nz/Medicines/infoSearch.asp.

For example, the Arrow - Fluoxetine data sheet [2] includes information from pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressant medicines in 4400 children and adolescents with major depressive disorder, obsessive compulsive disorder or other psychiatric disorders. The analyses revealed an average risk of suicidal behaviour or suicidality to be 4% in patients treated with an antidepressant compared with 2% of patients given placebo. The doubling in risk of suicidality in children and adolescents with major depressive disorder who are taking antidepressants is already known. In addition, symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants.

The MARC provides expert advice on medical and scientific evaluations of medicines safety issues. These safety issues are referred to the MARC by Medsafe. Medsafe has not referred the study by Professor Peter Gøtzsche to the MARC for review. Further information on the MARC is available on the Medsafe website: www.medsafe.govt.nz/committees/marc.asp.

5. Do Medsafe and MARC consider Professor Gotzsche and the Nordic Cochrane Centre have expertise in conducting meta analyses of data and if not, why not?

Medsafe notes that the Nordic Cochrane Centre may be well regarded in the field of meta-analysis and systematic review. Medsafe does not have any information on Professor Gøtzsche's expertise in conducting meta-analyses.

A major strength of systematic reviews and meta-analyses is their ability to pool data from individual studies leading to a larger sample size and more precise estimates. However, a key limitation is that they produce estimates that are only as reliable as the included studies.

6. What action if any have Medsafe and MARC taken in response to the finding of the Suicide Mortality Review Committee that 50% of their sample of adult males and mental health service users who died from suicide had a current prescription for antidepressants. If no action has been taken, why not?

Medsafe was not made aware of the Suicide Mortality Review Committee's (SuMRC) finding. Therefore, no action has been taken by Medsafe and this finding has not been referred to the MARC for advice. The significance of the SuMRC findings are wider than the use of medicines and are being considered by other departments in the Ministry of Health.

7. Did the Suicide Mortality Review Committee bring the above data to the attention of Medsafe or MARC?

The SuMRC did not bring the above data to the attention of Medsafe or MARC.

8. Do Medsafe consider the data on the use of pharmaceutical drugs by those who died from suicide in the SuMRC sample a signal and if so, what action does Medsafe intend to take to investigate the causal relationship between these drugs and suicide deaths?

It is always difficult to investigate the relationship between use of a medicine and any particular outcome through case reports. Causality assessments are conducted on spontaneous reports received by CARM using the World Health Organization causality assessment criteria (www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf). This assessment should be viewed more as a signal detection tool than a determination of whether a medicine caused an adverse reaction.

CARM notifies Medsafe if they identify a safety signal from spontaneous reports. Further review and investigation is then undertaken to determine whether the signal is real and if any action is required to manage the safety of the medicine.

Findings from the SuMRC's Feasibility Study will be used in the development of the Ministry of Health's new Suicide Prevention Strategy and Action Plan. Further information is publicly available on the Ministry of Health's website: www.health.govt.nz/our-work/mental-health-and-addictions/working-prevent-suicide/what-government-doing-prevent-suicide.

The best way of determining a link between a medicine and a reaction is through a randomised controlled study or a well conducted meta-analysis.

9. Does Medsafe consider that the provision of genotyping results which showed whether a person was a poor, intermediate, extensive or ultra-rapid metaboliser would be useful in conducting causality assessments for adverse reaction reports. Would, for example, the provision of a genotype for CYP4502D6 assist with identifying a biologically plausible mechanism for an individuals adverse reaction to drugs that are substrates of this enzyme? If this information was provided by consumers or others would Medsafe use it in conducting causality assessments?

The provision of genotyping results specific to the metabolism of medicines would be useful particularly for CARM's causality assessments of spontaneous adverse reaction reports. If this information was provided, it could be used to assist in conducting causality assessments.

I trust this information fulfils your request.

Yours sincerely

[redacted]

Group Manager
Medsafe

References

1. Sharma, T., et al., *Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports.* BMJ : British Medical Journal, 2016. **352**: p. i65.
2. Actavis New Zealand Limited. *Arrow - Fluoxetine New Zealand Data Sheet*. 20 August 2014 [Accessed 1 March 2017]; Available from: www.medsafe.govt.nz/profs/Datasheet/a/arrowfluoxetinetab.pdf.

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Report Title: **Coroners Cases**
Official Information Act Request

Prepared for: **Medsafe**

Prepared by: **New Zealand Pharmacovigilance Centre**
17 October 2016

Specific Request: "How many suspected adverse reaction reports have CARM received from Coroners since 2000 and how many of these related to SSRIs and/or suicide deaths?" [Question 2 of 9]

Results

NZPhvC has interpreted this request as:

Cases reported to CARM from 01 January 2000 through to 31 December 2016
Submitted by a Coroner or Coronial Services Unit

Number of Coroners cases since 2000	43
Number of Coroners cases since 2000 with SSRIs	4
Number of Coroners cases since 2000 with Suicide	7
Number of Coroners cases since 2000 with SSRIs and Suicides	2