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MANATŪ HAUORA

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Dabigatran etexilate (Pradaxa): Summary of reports to CARM

The funding of Pradaxa by Pharmac on 1 July 2011 has created a great deal of interest among healthcare professionals and the public. In turn this has stimulated the reporting of suspected adverse reactions associated with Pradaxa to the Centre for Adverse Reactions Monitoring (CARM).

Early data indicates that about 10,000 patients started dabigatran treatment up until the end of September 2011.

As of 7 November 2011 there were 295 reports in the CARM database detailing *suspected* adverse reactions to dabigatran. These reports were distributed across the different body systems as outlined in table 1. A suspected adverse reaction does not necessarily mean that the medicine caused the reaction, merely that the reporter suspected it may have.

Table 1: Distribution of reported *suspected* reactions to dabigatran

Category#	Total number of reactions*
Alimentary	256
Application site	1
Cardiovascular	41
Endocrine/Metabolic	8
Haematological	27
Musculoskeletal	14
Nervous System	37
Other	28
Procedure Related	20
Product Related	2
Psychiatric Changes	35
Reproductive disorders	1
Resistance Mechanism Disorders	2
Respiratory	31
Skin & appendages	28
Special Senses	3
Urinary	28

\# CARM classification

* The number of reactions is greater than the number of reports as one report may include one or more *suspected* reactions.

Gastrointestinal reactions were the most common adverse events reported. These reports (excluding cases of bleeds) accounted for 42% of all reports (124/295). The majority of reactions reported were considered non-serious by CARM and may be expected based on clinical data provided in the report, in addition to being described in the data sheet.

The eleven most commonly reported *suspected* adverse reactions are outlined in Table 2 on page 30.

There were a total of 20 medication errors reported to CARM. These reports generally described cases where the patient was either incorrectly switched from warfarin, given the incorrect dose for their age, or should not have been treated with dabigatran at all, such as those with severe renal impairment. The majority of these reports were received within the first few weeks of funding. Since the beginning of October only two reports of medication error were received.

Of the 295 reports, 78 (26%) were considered serious by CARM, as detailed in Figure 1.

Figure 1: Dabigatran serious reports

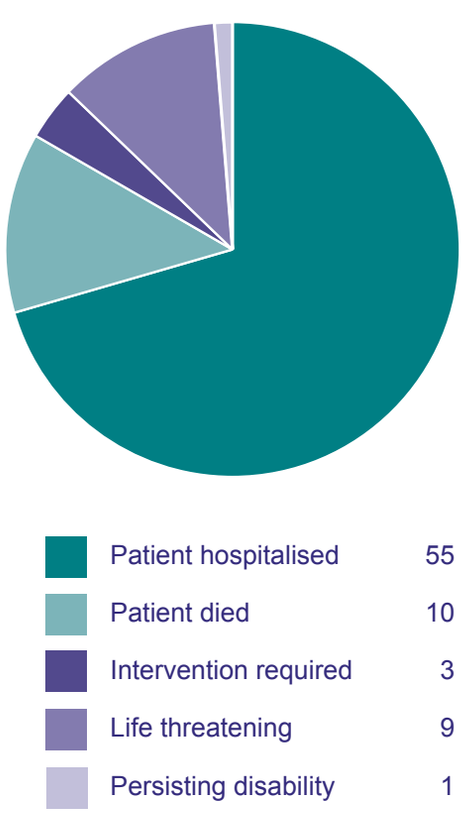

Table 2: Most commonly reported *suspected* adverse reactions to dabigatran

Adverse event	Number	Category
Dyspepsia	60	Alimentary
Rectal bleeding	47	Alimentary
Diarrhoea	26	Alimentary
Melaena	24	Alimentary
Medication error	20	Procedure Related
Abdominal pain	19	Alimentary
Haematuria	17	Urinary
Headache	14	Nervous System
Gastroesophageal reflux	13	Alimentary
GI haemorrhage	13	Alimentary
Dyspnoea	13	Respiratory

CARM considered that in all of the fatal cases received up to 7 November 2011, the death was unrelated to treatment with dabigatran. In these cases the death was attributed to another medicine or unrelated event such as pneumonia.

Adverse reaction data indicates that bleeding is the most important risk associated with dabigatran, specifically:

- Overall 42% (124/295) of the reports mentioned bleeding as a possible adverse reaction.
- Fifty-one (65%) of the 78 serious cases mentioned a bleeding event.
- Forty-one percent (51/124) of all cases mentioning bleeding as an adverse reaction were serious.
- In 29 of the serious cases (57%) the patient was also taking another medicine which can cause bleeding.
- Of all the serious cases more than half were reported in patients aged 80 years or above.

Medsafe has reviewed the incidence of adverse reactions in elderly patients. To date the data indicates there is a slightly higher incidence of reports of suspected adverse reactions in patients aged 80 years and above. Medsafe continues to closely monitor the safety of dabigatran in older patients.

When assessing the risks associated with dabigatran, an obvious medicine to compare it with is warfarin. A comparison using spontaneous adverse reaction reports is not strictly advisable due to the length of time warfarin has been available and the stimulated reporting of suspected adverse reactions to dabigatran. However, a crude comparison does provide some context for readers.

In the period between 1 Jan 2006 and 31 Dec 2010, CARM received 127 adverse reaction reports for warfarin. Sixty-five percent of these reports were considered to be serious, including 15 fatal reports. Of these fatal reports, CARM considered that warfarin had contributed to the patient's death in 11 cases.

The global number of adverse reaction describing serious bleeds, including New Zealand data, is noted to be lower than that seen in the clinical studies published to date. Healthcare professionals are reminded that all anticoagulants have risks including the risk of bleeding, and patients taking these medicines should be closely monitored for signs of bleeding.

Please continue to report all suspected adverse reactions to any anticoagulant to CARM.

M² update: Quetiapine and cardiomyopathy – an emerging safety signal

M² is a new medicines monitoring scheme that aims to stimulate adverse reaction reports for specific medicines and reactions; this helps Medsafe and CARM to investigate these safety signals and decide if any action needs to be taken.

The first medicine and reaction of interest added to the M² scheme was quetiapine and cardiomyopathy. Over a six month period Medsafe and CARM monitored reports received for the combination and further investigated this emerging safety signal.

Quetiapine is approved for use in New Zealand for the treatment of acute and chronic psychoses (including schizophrenia), and bipolar affective disorder. Quetiapine is structurally related to clozapine and olanzapine; clozapine has previously been associated with cases of myocarditis and cardiomyopathy.

Cardiomyopathy is a heart muscle disorder that can result in congestive heart failure.* Dilated cardiomyopathy (DCM) is the most common form and is also commonly associated with the use of medicines. Up to two thirds of cases are considered to be idiopathic; however identification of a precipitating cause is important. There is some evidence that DCM may be partially reversible if the precipitating cause is withdrawn.[1]

CARM has received 7 reports of cardiomyopathy associated with the use of quetiapine. These reports describe quetiapine being used for depression (3), bipolar disorder (2), and schizophrenia (2). The age range of patients was 20-52 years, and duration of quetiapine use was 6 months to 5 years. A total of 2 reports were confounded (1 by clozapine use and 1 by excessive alcohol consumption) and one patient's symptoms improved despite continuing quetiapine.

A biologically plausible mechanism for this association is yet to be confirmed; however some authors have suggested that, as with clozapine, a hypersensitivity myocarditis is the likely mechanism. Quetiapine may also have an indirect effect on the development of cardiomyopathy by causing obesity and diabetes.

The New Zealand quetiapine data sheets are in the process of being updated to indicate that cardiomyopathy has been reported in patients taking quetiapine.

Health professionals are advised to consider quetiapine as a possible cause in patients presenting with unexplained cardiomyopathy. Specialist advice should be sought and consideration given to discontinuing quetiapine treatment if cardiomyopathy occurs.

Please continue to report all suspected cases of cardiomyopathy associated with the use of quetiapine to CARM. This will help Medsafe to further explore this signal.

Your support of M² and New Zealand's spontaneous reporting scheme helps Medsafe to monitor and improve the safety of medicines in New Zealand.

** Excludes cardiac dysfunction resulting from structural heart disease, such as coronary artery disease, primary valve disease or severe hypertension.*

References

1. Stevenson LW, Loscalzo J. Chapter 238. Cardiomyopathy and Myocarditis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine.* 18th ed. New York: McGraw-Hill; 2011. **http://www.accessmedicine.com/content.aspx?aID=9127313** Accessed November 16, 2011.

SSRIs – still associated with cases of bleeding

Healthcare professionals are reminded that selective serotonin reuptake inhibitors (SSRIs*) increase the risk of bleeding, possibly due to altering platelet function. Haemorrhages reported in association with the use of SSRIs include bruising, purpura, epistaxis, and peri-operative, vaginal, and gastrointestinal bleeding.[1]

CARM continues to receive reports of bleeds in which SSRIs have been identified as being a co-suspect medicine or may have contributed to the bleed. One such report describes a patient who experienced a subdural haematoma with severe consequences while taking warfarin and an SSRI. Importantly, the patient's INR was found to be within the normal range.

The risk of bleeding appears to be higher when SSRIs are used with other medicines that are known to increase the risk of bleeding, such as anticoagulants and NSAIDs. Combining any SSRI and NSAIDs is thought to result in 1 in 250 patients experiencing an upper GI bleed if no acid suppressant agent is used.[2]

Healthcare professionals are advised to use caution when considering co-prescribing an SSRI with an anticoagulant or NSAIDs. Should an SSRI need to be prescribed with a NSAID, a proton pump inhibitor should also be considered.

Prescribers are recommended to inform patients to closely monitor for signs of bleeding and to seek urgent advice should this occur.

** The bleeding risk also applies to Venlafaxine, a Selective Serotonin Noradrenaline Reuptake Inhibitor (SNRI) with similar properties to the SSRIs.*

References

1. Prescriber Update. Increased risk of bleeding with SSRIs. Prescriber Update 2006; 27(2): 18-20.
2. De Abajo FJ, Garcia-Rodriguez LA, et al. 2008. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid suppressive agents. Arch Gen Psychiatry: 65: 795-803.

Alert: Safety of Ayurvedic products – reports of lead poisoning

Recent testing by the Institute of Environmental Science and Research (ESR) has identified that some ayurvedic products used in New Zealand contain high levels of lead.

Medsafe initiated testing after a patient was hospitalised with lead poisoning. The source of lead was found by the Auckland Regional Public Health Service as being via the ingestion of an ayurvedic product. This product had been supplied to the patient by a New Zealand based ayurvedic practitioner.

Ayurvedic medicine is a type of traditional medicine native to India. In Western countries it is considered a form of complementary medicine. The aim of ayurvedic medicine is to integrate and balance the body, mind, soul and spirit. This is thought to help in preventing illness and promote well being. Heavy metals are commonly incorporated into ayurvedic products for a therapeutic effect.

ESR tested seven products and found that all contained lead. Five of those tested contained lead in sufficient quantities to be considered prescription medicines, with two products found to contain dangerously high levels (up to 57mcg per tablet). The product names are:

- Ziety
- Puspadhanwa Ras
- Ekangvir Ras
- Vatgajankush Ras
- Makardhwaj Bati

These products were all imported into New Zealand by an ayurvedic practitioner. In addition to lead being found in the products, arsenic and mercury were also found to be present in a number of products.

Key messages and advice

The Environmental Health Team from the Auckland Regional Public Health Service advises consumers to:

- Be cautious when purchasing herbal products from local shops or when obtaining medicines from overseas. Only purchase medicines where the contents are clearly listed and known to be safe.
- Consult your doctor or pharmacist before taking an ayurvedic remedy.
- Seek immediate medical attention if you become unwell while taking an ayurvedic product.

Medsafe is working with ayurvedic practitioner organisations to provide education regarding the risks associated with ingesting high levels of heavy metals, and to prevent practitioners from importing products that pose a threat to the health of their patients.

Healthcare professionals are encouraged to ask patients about their use of complementary and alternative medicines, and to report all suspected adverse reactions to CARM.

Modafinil safety review – a wake up call

Medsafe has recently completed a safety review of modafinil, a medicine that promotes wakefulness but the precise mechanism of action remains unclear.

Medsafe has concluded that the benefits of treatment outweigh the potential risks when used:

- To improve wakefulness in patients with excessive daytime sleepiness (EDS) associated with narcolepsy.
- To treat EDS associated with moderate to severe chronic shift work sleep disorder (SWSD) where non-pharmacological interventions are unsuccessful or inappropriate.
- As an adjunct to continuous positive airways pressure (CPAP) to treat excessive daytime sleepiness in patients with obstructive sleep apnoea hypopnoea syndrome (OSAHS).

The Australian medicines regulator (TGA) has also recently confirmed that the balance of risks and benefits of modafinil is positive when used for these indications.[1]

The Modavigil (modafinil) datasheet is being updated to include more information about the risk of multi-organ hypersensitivity reactions, serious skin reactions, psychiatric disorders, cardiovascular disease, and the potential for dependence.

Prescribers are encouraged to familiarise themselves with the complete prescribing information for modafinil available on the Medsafe website at **www.medsafe.govt.nz.**

Key messages for healthcare professionals:

- Modafinil treatment should be initiated and supervised by physicians with experience in sleep disorders such as neurologists or respiratory specialists.
- Modafinil is contraindicated for use in pregnancy and is not approved for use in children or adolescents for any indication.
- The development of skin and hypersensitivity reactions, central nervous system, psychiatric and cardiovascular system adverse reactions appears to be related to higher doses of modafinil. Therefore, modafinil should always be started and maintained at the lowest possible dose.
- The effectiveness of oral contraceptives may be impaired in patients receiving modafinil due to the induction of the CYP 3A4 enzyme system.
- PHARMAC currently subsidises modafinil (under special authority criteria) for the treatment of EDS associated with narcolepsy only.[2]

Please continue to report all suspected serious or unexpected adverse reactions to modafinil to CARM.

References

1. TGA (2011). Modafinil (Modavigil) – safety update. Medicines Safety Update Volume 2, Number 5, October 2011. Available at **http://www.australianprescriber.com/magazine/34/5/148/51**
2. PHARMAC (2011). Application for subsidy by special authority.

MARC's Remarks: September meeting

The Medicines Adverse Reactions Committee (MARC) met on 8 September 2011 and made the following recommendations:

The MARC considers the risk benefit balance of **varenicline** (Champix) treatment remains positive following a review of studies suggesting varenicline increases the risk of patients experiencing **cardiovascular events**. The MARC concluded that data available to date does not demonstrate a causal association; however the medicine data sheet has now been updated to provide more information about reports of cardiovascular events in patients taking varenicline.

The MARC reviewed a recently published meta-analysis that suggested an increased risk of **mortality** in COPD patients using **tiotropium** (Spiriva). There are two formulations of Spiriva inhalers – HandiHaler and Respimat; however only the HandiHaler formulation is marketed in New Zealand. The MARC considered that the possibility of an increased mortality risk may be present for the Respimat formulation but not the HandiHaler formulation.

The MARC reviewed recently published data on the risk of bladder cancer associated with the use of **pioglitazone** and considered that this data does not support a causal association. However, they agreed that it was not possible to rule this association out completely so recommended that the medicine datasheet be updated to raise awareness of this potential safety issue to healthcare professionals.

The MARC reviewed the use of **oral ketoconazole (Nizoral)** following its suspension in France following concerns it causes **hepatotoxicity**. The Committee noted that anti-fungals are commonly known to be associated with hepatic injury, with ketoconazole known to exhibit a higher risk that other agents in its class. The French review did not appear to identify any new safety data, with the MARC noting that this adverse reaction is clearly described in the New Zealand datasheet.

The Committee noted that a case of **tachycardia** had been reported in a patient with pre-existing heart failure treated with cyclizine. Although the use of cyclizine in patients with heart failure is already cautioned, the MARC considered that this report serves as a useful reminder to healthcare professionals of this adverse effect.

Further information about all of these issues can be found in the meeting minutes, available at: **www.medsafe.govt.nz/profs/adverse/Minutes147.htm**

Complementary Corner: Essential oils associated with seizures

Essential oils, obtained from plants, are widely used in aromatherapy and are included in some medicines. Healthcare professionals are reminded that these substances, when administered orally or topically, can rarely cause seizures in young children and in those patients with epilepsy.[1]

The essential oils generally associated with seizures include:[1]

Essential Oil	Species
Eucalyptus	*Eucalyptus globulus*
Fennel	*Foeniculum vulgare*
Hyssop	*Hyssopus offiicinialis*
Pennyroyal	*Mentha pulegium or Hedeoma pulegioides*
Rosemary	*Rosemarinus officinalis*
Sage	*Salvia officinalis*
Savin	*Juiperus Sabina*
Tansy	*Tanacetum vulgare*
Thuja	*Thuya occidentalis*
Turpentine	*Pinus species*
Wormwood	*Artemisia absinthium*

Active substances contained within camphor, thujone and cineole have also been associated with seizures. In addition to the substances listed above, there is also a report in the literature of clove oil causing fits, coma, coagulopathy and acute liver damage after unintentional exposure in a two-year-old.[2]

Healthcare professionals are reminded that many over-the-counter products contain essential oils. For example there have been reports of seizures in children who have unintentionally consumed products such as Vicks vapour rub.[3]

Importantly, seizures have been reported when products have been taken orally or following topical use. An adverse reaction report received

recently in New Zealand describes vomiting, lethargy and ataxia followed by a grand mal seizure in a 4-year-old girl who was treated with an over-the-counter head lice treatment containing eucalyptus oil.[4]

The potential of exposure to a product containing an essential oil should be considered in any case of a first seizure of unexplained origin. In addition, patients with epilepsy should be warned of the risk of seizure following exposure to these substances.

While the risk of seizure appears to be very low, it is likely that adverse reactions to complementary and over-the-counter medicines are rarely reported. Lack of reporting may be due to public and healthcare professional perception that these products are safe, and/or a lack of knowledge by consumers about where to report problems.

Any suspected adverse reaction to complementary medicines and over-the-counter medicines should be reported to CARM.

References

1. Burkhard PR, Burkhardt K, Haenggeli C-A et al 1999 'Plant-induced seizures: reappearance of an old problem' J *Neurol* **246:** 667-670.
2. Hartnoll G, Moore D, Douek D 1993 ' Near fatal ingestion of oil of cloves' *Arch Dis Childhood* **69:** 392-393.
3. Flaman Z, Pellechia-Clarke S, Bailey B et al 2001 'Unintentional exposure of young children to camphor and eucalyptus oils' *Paediatr Child Health* **6:** 80-83.
4. Waldman N 2011 'Seizure caused by dermal application of over-the-counter eucalyptus oil head lice preparation' *Clin Toxicol* **49:** 750-1.

Update: Erectile dysfunction medicines being imported into New Zealand

Healthcare professionals are advised that consumers continue to purchase and import erectile dysfunction products that have been contaminated with undisclosed prescription medicines or are counterfeit.

Products sold in New Zealand

In October this year the Director-General of Health advised consumers to immediately stop taking two products for erectile dysfunction as they were found to contain undeclared prescription medicines. These particular products were sold as herbal remedies and were marketed as "Get Stiff" and "Maxi Mize".

The October alert is the latest of a series of alerts that have been required in New Zealand in recent years. In the last year over 60 remedies, mostly purporting to be herbal, have been seized at the border, tested by Medsafe, and found to contain undeclared prescription medicines. These medicines are predominantly sildenafil, vardenafil, and tadalafil, or a combination of these active ingredients.

The adulterated products recalled in New Zealand have been sold in adult sex shops, herbal stores, and pharmacies. Consumers or healthcare professionals who suspect that a product may contain a prescription medicine should contact Medsafe's Compliance team for advice.

Imported packages

Since 2007 packages containing prescription medicines for the treatment of erectile dysfunction have been consistently the largest type of medicine referred to Medsafe by New Zealand Customs at the border.

Products generally contain either sildenafil, tadalafil, or vardenafil and generally fall within the following categories:

1. They are genuine products imported such as Viagra (sildenafil), Cialis (tadalafil), or Levitra (vardenafil).
2. They are generic brands that openly declare the ingredients.
3. They are counterfeit Viagra, Cialis or Levitra.
4. They are products purporting to be herbal remedies that are adulterated with hidden or undeclared medicines.

Counterfeit and adulterated products are destroyed immediately, while genuine medicines are able to be released to consumers once a valid prescription is provided to Medsafe. If a prescription is not produced, these packages are also destroyed. Further information about the importation of medicines is available on the Medsafe website at: **http://www.medsafe.govt.nz/Consumers/MIET/ImportMedicines.asp**

During 2010 a total of 11,930 parcels, originating from 114 different countries, were stopped by Customs and provided to Medsafe for inspection. Of these parcels Medsafe detained over 9000

prescription medicines, and gave the importer the opportunity to provide a prescription so the package could be released.

Of particular concern is that of 2623 medicines detained for the treatment of erectile dysfunction, only 894 were able to be released. This indicates that most products were purchased without a prescription or without the knowledge that they contained prescription medicines.

Health care professionals are advised to warn patients about the dangers of obtaining medicines over the internet, and to consider this possibility when patients present with unexplained symptoms that may actually be adverse effects.

Graseby syringe drivers – deadline passed

The deadline for the removal of Graseby MS-series syringe drivers has now passed. These devices should now have been removed from clinical use and replaced with an alternative.

Graseby MS-series syringe drivers still in clinical use need to be replaced immediately. Smiths Medical, suppliers of the Graseby devices, has now ceased the supply of spare parts and all service support for these devices in New Zealand.

Further information on the removal of Graseby syringe drivers can be found at: **http://www.medsafe.govt.nz/profs/device-issues.asp**

Specific questions regarding this matter should be directed to Robert Jelas at Medsafe (04 819 6881).

TEST YOUR KNOWLEDGE – end of year Prescriber Update quiz

Have you read your copy of *Prescriber Update in 2011?*
Have you kept up to date with emerging safety signals?
Test your knowledge with the end of year *Prescriber Update* quiz.

Answers to the quiz are available at: **www.medsafe.govt.nz/profs/PUarticles.asp**

1. Rosiglitazone was removed from the market in New Zealand because of:
   a. An increased risk of bladder cancer ☐
   b. The cost of treatment ☐
   c. An increased risk of myocardial infarction ☐
   d. An increased risk of pancreatitis ☐

2. Name the three medicines currently on the M[2] medicines monitoring programme.

3. Cough and cold medicines are contraindicated in which group?
   a. Elderly patients over 80 years ☐
   b. Children under 12 years of age ☐
   c. Children under 6 years of age ☐
   d. For the treatment of "man-flu" ☐

4. How can paroxetine reduce the effectiveness of tamoxifen?
   a. By reducing the absorption of tamoxifen ☐
   b. By inhibiting CYP2D6 – an enzyme involved in the production of an active metabolite of tamoxifen ☐
   c. Because paroxetine promotes cell growth ☐
   d. By inducing the metabolism and clearance of tamoxfen. ☐

5. Which CYP3A4 inhibitor increases the risk of patients experiencing an adverse reactions with statins:
   a. Erythromycin ☐
   b. Fluconazole ☐
   c. Ciclosporin ☐
   d. Amiodarone ☐
   e. All of the above ☐

6. The maximum recommended dose of simvastatin in New Zealand is now:
   a. 20 mg daily ☐
   b. 40 mg daily ☐
   c. 80 mg daily ☐
   d. 160 mg daily ☐

7. The recommended dose of dabigatran in patients with atrial fibrillation who are considered at risk of bleeding (ie elderly, concomitant anticoagulants) is:
   a. 150 mg twice daily ☐
   b. 150 mg once daily ☐
   c. 110 mg twice daily ☐
   d. 75 mg once daily ☐

8. True or false: daibgatran is contraindicated in patients with severe renal impairment (< 30 ml/min CrCl). T ☐ F ☐

9. Name two medicines associated with drug-induced glaucoma.
   a. .....
   b. .....

10. True or false: SSRIs do not increase the risk of bleeding T ☐ F ☐

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

Fax: (03) 479 7150
Phone: (03) 479 7247

Reporting form for Adverse Reactions to Medicines, Vaccines and Devices and all Clinical Events for IMMP

PATIENT DETAILS **HP3442**

Surname:	First Name/s:	NHI No:	
Address:		Date of Birth:	Sex:
		Ethnicity:	

ALL MEDICINES IN USE *ASTERISK SUSPECT MEDICINE/S* Include over-the-counter (OTC) and alternative medicines

Medicine or Vaccine+batch no. (and brand name if known)	Daily Dose	Route	Date Started	Date Stopped	Reason for Use

DESCRIPTION OF ADVERSE REACTION OR EVENT

Date of onset: _____

Recovered ☐ Not yet recovered but improved ☐ Not yet recovered ☐ Unknown ☐ Fatal ☐ - Date of Death: _____

Severe? - Yes ☐ No ☐ Rechallenged? - No ☐ Yes ☐ Result: _____

OTHER FACTORS - Please tick or specify as appropriate

Renal disease ☐ Allergy ☐: _____ Other Medical Conditions: _____

Hepatic disease ☐ Nutritional Suppl or OTC use ☐ : _____ Industrial Chemicals ☐: _____

REPORTER - Please tick as appropriate: Doctor ☐ Pharmacist ☐ Dentist ☐ Nurse ☐ Other ☐: _____

Name:

Address: Signature: _____

Phone: _____ Date: _____

Send completed form to CARM

Freepost 112002, CARM, PO Box 913, Dunedin 9054 **or** Fax: (03) 479 7150

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