ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (7): 605-613
0114-5916/10/0007-0605/$49.95/0

Fatal and Non-Fatal Cardiovascular Events in a General Population Prescribed Sibutramine in New Zealand

A Prospective Cohort Study

Mira Harrison-Woolrych,[1] *Janelle Ashton*[1] and *Peter Herbison*[2]

1 Intensive Medicines Monitoring Programme, Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand
2 Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand

Abstract

Background: The cardiovascular safety of sibutramine is currently under review by medicines regulatory authorities worldwide after the SCOUT (Sibutramine Cardiovascular Outcome Trial) showed an increased risk of cardiovascular events in patients taking sibutramine. Further data regarding the cardiovascular safety of sibutramine in a general population are now required.

Objective: To quantify the risk of fatal and non-fatal cardiovascular adverse events in a general population prescribed sibutramine in postmarketing use.

Study Design: Observational prospective cohort study of patients dispensed sibutramine during a 3-year period (2001–4) and followed up for at least 1 year after their last prescription. The study included record-linkage to national mortality datasets to identify fatal events.

Setting: Postmarketing 'real-life' use of sibutramine in a general population in New Zealand.

Patients: All New Zealand patients dispensed a prescription for sibutramine in a 3-year period (for whom a National Health Identification number could be validated). 15 686 patients were included in the record linkage study for fatal events. A subgroup of 9471 patients was followed up by intensive methods for non-fatal events.

Main Outcome Measures: (i) Rate of death from all causes and from cardiovascular events; and (ii) rates of non-fatal cardiovascular adverse events.

Results: Total exposure to sibutramine for 15 686 patients in the validated cohort was 5431 treatment-years. The rate of death from all causes in this cohort was 0.13 (95% CI 0.05, 0.27) per 100 treatment-years exposure. The rate of death from a cardiovascular event was 0.07 (95% CI 0.02, 0.19) per 100 treatment-years exposure. The most frequent non-fatal cardiovascular events in the intensively followed up cohort were hypertension, palpitations, hypotensive events and tachycardia.

Conclusions: Risk of death from a cardiovascular event in this general population of patients prescribed sibutramine was lower than has been reported in other overweight/obese populations. The results of this study suggest that further evaluation of the benefit-risk profile of sibutramine is now required.

Background

Sibutramine (Meridia®, Reductil®) is a serotonin-noradrenaline (norepinephrine) reuptake inhibitor that has been marketed worldwide for the management of obesity. The cardiovascular safety of this medicine has been an issue of concern and recently the European Medicines Agency recommended that the marketing authorizations for sibutramine should be suspended because of an increased risk of cardiovascular events.[1] In the US, sibutramine remains available but the FDA has requested that new contraindications for patients with a history of cardiovascular disease should be added to the sibutramine label.[2] These regulatory actions followed review of results from the SCOUT (Sibutramine Cardiovascular Outcome Trial), which showed an increased risk of serious, non-fatal cardiovascular events in patients at high risk of cardiovascular disease who were taking sibutramine compared with those taking placebo.[3]

The cardiovascular safety of sibutramine has been an issue of concern since 2002 when it was withdrawn from the market in Italy following reports of deaths and other cardiovascular events.[4] However, the product's European marketing approval was subsequently re-instated a few months later, following benefit-risk reviews by several regulatory authorities, including the FDA and Health Canada.[5] In New Zealand, sibutramine has been marketed since 2001 and its postmarketing safety was monitored by the Intensive Medicines Monitoring Programme (IMMP).[6] In 2006, the IMMP published a signal of QT prolongation associated with sibutramine,[7] after identifying reports of palpitations associated with syncope or collapse.

Concerns about cardiovascular risk with sibutramine persist[8] and the product continues to be marketed in the US, Australia, New Zealand and other countries for overweight and obese patients without a history of cardiovascular disease. More data are now required to understand the cardiovascular risks of this medicine in a general population in a 'real-life' clinical setting. To this end, we have undertaken analyses of fatal and non-fatal cardiovascular events identified during the time that sibutramine was intensively monitored in New Zealand.

Methods

The IMMP performs prospective observational cohort studies on selected medicines using prescription event monitoring, and its methods have been described in detail previously.[6] In brief, the cohort of patients for each monitored medicine is established from dispensing data collected at regular intervals directly from pharmacies throughout New Zealand. Information collected from these dispensing records includes the name, address, National Health Identification (NHI) number (a unique identifier of healthcare users in New Zealand), sex and date of birth of the patient, prescriber identification and details of the monitored medicine, including dispensing dates, dose and quantity dispensed.

Patients dispensed the monitored medicines are followed up by multiple 'intensive' methods, including follow-up questionnaires, record linkage to national datasets (see Record Linkage for Fatal Events section) and assessment of other safety information received by the IMMP.[6] As the IMMP operates within the New Zealand Pharmacovigilance Centre,[6,9] information for patients taking the monitored medicines is also received in the form of spontaneous reports ('yellow cards') sent to the national centre by health professionals, pharmaceutical companies and patients.[9] All spontaneous reports for the monitored medicines are assessed by IMMP

clinical staff (as described in the Sibutramine Study section below) and these adverse events are included in the IMMP datasets for analysis.

The primary method of patient follow-up in the IMMP is by follow-up questionnaires that are proactively sent to the prescribing doctor – usually the patient's general practitioner – in the period after the medicine has been dispensed.[6] IMMP questionnaires request information on all new clinical events since the patient started the monitored medicine. Doctors are asked to record (in summary form) all entries from the patients' notes from the start date of the medicine. Other information specific to the monitored medicine is also requested and may include details of past medical history and concomitant medications.

Sibutramine Study

Monitoring of sibutramine began on 1 February 2001 when marketing of this medicine commenced in New Zealand. Prescription data collection continued until 31 March 2004, a period of 38 months, at which time the cohort was closed. Follow-up questionnaires were sent to doctors in March 2002 and November 2003 for patients with a first prescription of sibutramine issued up to 30 November 2002, and this group formed the intensively followed-up population for this study (see Analyses section). In addition to requesting information on adverse clinical events, the follow-up questionnaires for sibutramine requested information on the patient's weight/height/body mass index (BMI).

Returned questionnaires and other follow-up information were assessed by clinical staff at the IMMP. All adverse events identified were coded using terms from a specialized dictionary based on the WHO Adverse Reaction Terminology (WHO-ART)[6] and grouped into System Organ Classes (SOCs). For every adverse event identified (including fatal events) causality assessments were performed[9] to determine the relationship of the event with sibutramine.[6] For the cardiovascular event analyses performed in this study, all adverse events were included, whether or not they had been assessed as causally associated with the medicine. Events within the Cardiovascular SOC were placed into clinical subgroups (e.g. hypertensive events, myocardial ischaemia events, etc.) for further interpretation and analysis. For deaths identified during the monitoring study, additional follow-up information was sought to confirm the cause of death and other details of the case.

Record Linkage for Fatal Events

The New Zealand Health Information Service (NZHIS) National Collections databases hold records of New Zealand patients, including details of births, deaths and hospital admissions.[10] A validation process was undertaken whereby details held for each patient in the IMMP sibutramine cohort were checked against the NZHIS database for name, sex and date of birth. Record linkage was then performed for this validated sibutramine cohort to identify all deaths of patients before 31 December 2005 (this date was chosen to allow at least a 1-year follow-up period between patients' last prescription for sibutramine and the time of death).

Having identified all recorded deaths of sibutramine patients from 1 February 2001 to 31 December 2005 as described, the time period from the date of each patient's last dose of sibutramine to the date of their death was calculated. Deaths that occurred more than 365 days after the patient's last dose of sibutramine were excluded from further analyses. For all deaths occurring within 1 year of taking sibutramine, information on the patient's cause of death was obtained from the NZHIS. These data are collated from information recorded on death certificates and may include information from post-mortems and coroners' enquiries if performed.[10] Information obtained for each case of death was assessed and included evaluation of information from national hospital admission records and IMMP follow-up questionnaires (where possible) to identify possible risk factors and confounding factors related to the patient's death.

Analyses

For calculation of the death rate in this cohort, the numerator was defined as the number of

deaths occurring whilst taking sibutramine or within 30 days of the last dose. The denominator was defined as total treatment-years exposure in this cohort. This was calculated from the accumulated days of treatment (derived from each patient's dispensing records) plus 30 days. Previous analyses have shown sibutramine is used in treatment courses,[11] and this was accounted for by calculating treatment duration for each course plus 30 days.

Rates of non-fatal cardiovascular adverse events per 1000 patients exposed were calculated for three denominator populations within the sibutramine cohort.

1. The total validated cohort as defined above.
2. The subgroup of the cohort who had received a sibutramine prescription up to 30 November 2002 who were termed the 'followed-up population'. This group included patients for whom follow-up information was sought by questionnaires and those on whom other follow-up information was received (e.g. spontaneous report).
3. The subgroup of the followed-up population for whom follow-up questionnaires had been returned. This last group was termed 'the responder population'.

Results

The total IMMP cohort for sibutramine dispensings between 1 February 2001 and 31 March 2004 included 17 298 patients. A valid NHI number was identified for 15 686 patients (91% of the IMMP cohort); hereafter this is referred to as the validated cohort.

In the validated cohort there were 13 303 (84.8%) females and 2379 (15.2%) males. The age of the validated cohort ranged from 6 years to 90 years, with a mean age of 42.5 years (female mean = 42 years, male mean = 44.6 years) and a median age of 43 years (female median = 42 years, male median = 45 years).

BMI data were obtained for 1874 patients in the followed-up population of 9471 patients who received a sibutramine prescription up to 30 November 2002. Mean pre-treatment BMI in this subgroup was 34.3 kg/m^2 (SD 6.4 kg/m^2). This subgroup was tested against the validated cohort and had a similar age and sex distribution.

Total exposure to sibutramine for the validated cohort was 1 983 790 days (5431.32 treatment-years). Treatment duration ranged from 1 day to 1080 days (2.96 years), with a median exposure of 60 days.

Fatal Events

For the validated cohort of 15 686 patients, 82 deaths were identified to 31 December 2005. Of these, 26 deaths occurred within 365 days of the patients' last dose of sibutramine, and 56 were excluded from further analyses. Causes of death and other clinical information were reviewed for the 26 patients who died within 1 year of taking sibutramine. Of these, seven patients died while taking sibutramine or within 30 days of the last dose. Causes of death for these seven patients are shown in table I.

Four of the seven deaths were from cardiovascular events: two patients had fatal strokes, one had an acute myocardial infarction and one died from a pulmonary embolism.

The rate of death from all causes in the validated sibutramine cohort was 0.13 (95% CI 0.05, 0.27) per 100 treatment-years exposure. The rate of death from a cardiovascular event was 0.07 (95% CI 0.02, 0.19) per 100 treatment-years exposure.

Non-Fatal Cardiovascular Events

In the validated sibutramine cohort there were a total of 1322 adverse events; of these, 191 (14%) were assessed as cardiovascular events. The 191 cardiovascular events were identified in 150 patients. Of these, four resulted in death of the patient (see Fatal Events section) and were excluded from this analysis. The rates of non-fatal cardiovascular events per 1000 patients in each of the three IMMP populations (as defined in the Analyses section) are shown in table II. Hypertension (primarily new onset after starting sibutramine), palpitations, hypotensive events and tachycardia were the most commonly reported cardiovascular events.

Table I. Summary of deaths of sibutramine patients within 30 days of last dose

Case no.	Age (years)	Sex	Dose (mg)	Time to death[a] (days)	Treatment duration (days)[b]	CoD[c] diagnosis 1	CoD diagnosis 2	Risk factors[d]	Outcome[e]
1	71	F	10	On med	87	Cerebrovascular accident	Metastastic pancreatic carcinoma	Carcinoma, previous VTE	C
2	71	M	10	On med	10	Acute myocardial infarction	Hypertension, atherosclerosis	Type 2 diabetes mellitus, end-stage renal disease, cerebral infarct	C
3	51	M	10	On med	14	Motor vehicle accident	Nil recorded	Nil known	N
4	54	M	10	12	30	Haemorrhagic stroke	Hypertension	Hypertension	C
5	44	M	10	14	90	Meningococcal septicaemia	Nil recorded	Nil known	N
6	41	F	10	27	120	Aeroplane accident	Nil recorded	Nil known	N
7	60	F	10	30	30	Pulmonary embolism	Nil recorded	Recent GP visit for chest pain	N

a Time to death = time from last dose of sibutramine to date of death.

b Treatment duration calculated as accumulated days of dispensing or time from first dispensing date to time of death (if shorter).

c As derived from NZHIS datasets.

d Risk factors for patient's death, derived from NZHIS records and information from IMMP case notes for each patient (follow-up questionnaires, spontaneous reports, pharmacy reports, other data).

e IMMP assessment of outcome (see Methods section).

C = died, medicine may have been contributory; **CoD** = cause of death; **diagnosis 1** = first cause of death; **diagnosis 2** = second cause of death; **F** = female; **GP** = general practitioner; **IMMP** = Intensive Medicines Monitoring Programme; **M** = male; **N** = died, unrelated to the medicine; **NZHIS** = New Zealand Health Information Service; **On med** = died whilst still taking sibutramine; **VTE** = venous thromboembolism.

Discussion

The cardiovascular risks of sibutramine have been an issue of concern for some years, but assessment of spontaneous reports of deaths or other serious cardiovascular events has been difficult for several reasons. Perhaps most importantly, the condition for which sibutramine is licensed (overweight/obesity) is itself a major risk factor for cardiovascular disease.[12] The design of the SCOUT study (a randomized, placebo-controlled trial[13]) accounted for this important confounder and demonstrated an increased risk of serious, non-fatal cardiovascular events in patients with an increased risk of cardiovascular disease taking sibutramine compared with placebo.[2,3] The SCOUT study also reported an overall risk of death of 1.2 per 100 years of sibutramine exposure,[3] which is approximately 10-fold higher than the estimated rate of death reported in this IMMP study.

Although review of the SCOUT study results led to suspension of sibutramine in Europe,[2] there are several reasons why the results of that clinical trial may not be generalized to populations of patients who have been prescribed sibutramine in 'real-life' postmarketing use. First, SCOUT recruited a specific high-risk group of overweight/obese patients with an increased risk of cardiovascular disease. Such patients have been contraindicated from sibutramine use in New Zealand[14] and are now contraindicated in the US.[1] However, contraindications on the product label do not always prevent use of a medicine by such patients in 'real life' use. Assessment of the cases of death in this IMMP study identified that some patients had conditions (e.g. pre-existing hypertension) that should perhaps have contraindicated use of sibutramine.

An important difference between the study population in SCOUT and this IMMP cohort was patient age. The median age of subjects in SCOUT was 63 years[3] compared with 43 years in the IMMP study population. As age is one of the most important independent risk factors for

Table II. Non-fatal cardiovascular events per 1000 patients in the Intensive Medicines Monitoring Programme (IMMP) sibutramine cohort

Cardiovascular event[a]	Validated cohort[b] (N = 15 686)		Followed-up population[c] (N = 9471)		Responder population[d] (N = 3982)	
	no.	rate/1000	no.	rate/1000	no.	rate/1000
Hypertension	65	4.14	64	6.76	59	14.82
new onset hypertension	61	3.89	60	6.33	55	13.81
hypertension worse	4	0.26	4	0.42	4	1.00
Cardiac dysrhythmias	60	3.83	55	5.81	44	11.05
tachycardia	22	1.40	20	2.11	16	4.02
palpitations	31	1.98	28	2.96	24	6.03
SVT	2	0.13	2	0.21	1	0.25
PAT	0	ND	1	0.11	1	0.25
atrial fibrillation	2	0.13	2	0.21	1	0.25
ectopic beats	2	0.13	1	0.11	1	0.25
QT prolonged	1	0.06	1	0.11	0	ND
Hypotensive events	29	1.85	26	2.75	22	5.52
dizziness	18	1.15	16	1.69	13	3.26
faintness	5	0.32	4	0.42	4	1.00
hypotension	3	0.19	3	0.32	3	0.75
syncope	1	0.06	1	0.11	1	0.25
circulatory collapse	2	0.13	2	0.21	1	0.25
Myocardial ischaemia	17	1.08	17	1.79	14	3.52
angina	1	0.06	2	0.21	1	0.25
cardiac chest pain	11	0.70	11	1.16	10	2.51
chest tightness	3	0.19	3	0.32	3	0.75
t-wave inversion	1	0.06	1	0.11	0	ND
myocardial infarction	1	0.06	0	ND	0	ND
Cerebrovascular accident	3	0.19	2	0.21	2	0.50
cerebral thrombosis	1	0.06	1	0.11	1	0.25
stroke	1	0.06	1	0.11	1	0.25
TIA	1	0.06	0	ND	0	ND
Heart failure events	8	0.51	6	0.63	4	1.00
dyspnoea	3	0.19	3	0.32	2	0.50
congestive heart failure	1	0.06	1	0.11	1	0.25
peripheral oedema	4	0.26	2	0.21	1	0.25
Other	3	0.19	3	0.32	3	0.75

a Clinical events as coded using terms from the IMMP dictionary (see methods section for details).

b Patients for whom an NHI has been identified and validated against the NZHIS-NHI database details.

c Patients with a first prescription issued up to 30 November 2002 who were intensively followed up (see methods section for details). Patients in this group for whom a follow-up questionnaire was not returned may have had events reported by other methods, e.g. spontaneous report.

d Patients for whom a response to the IMMP follow-up questionnaire was received. The total number of responses received was 4052 for 3982 patients as some patients had more than one follow-up generated and returned.

ND = no data; **NHI** = National Health Identification; **NZHIS** = New Zealand Health Information Service; **PAT** = paroxysmal atrial tachycardia; **SVT** = supraventricular tachycardia; **TIA** = transient ischaemic attack.

cardiovascular disease, the 20-year difference between the two study populations may explain the higher rate of death observed in the SCOUT study. Other factors to be considered include patient sex, as over half the population in SCOUT was male, whereas the IMMP cohort was predominantly (85%) female. Another issue may be the period of observation as SCOUT has only reported the risk of death in the first 6 weeks of sibutramine treatment,[3] whereas this IMMP record linkage study has attempted to identify all deaths in a population taking sibutramine (for an average of 2 months, but with a wide range of treatment durations up to 3 years) and followed-up for at least 1 year.

These and other differences between clinical trials and 'real-life' postmarketing use were a key justification for performing this IMMP study. Our results reflect the risks observed in a nationwide population of almost 16 000 patients prescribed sibutramine over a 3-year period. Strengths of our study include its accurate determination of sibutramine exposure (records are obtained directly from pharmacy dispensings, which are preferable to prescription records or sales data) and the intensive follow-up of patients whilst taking the medicine and for at least 1 year after stopping. Record linkage to national mortality datasets is a useful method of identifying deaths in this population and the only deaths missed are likely to be those patients who moved away from New Zealand and might have died overseas.

Whilst comparisons between studies may be difficult because of differing study populations, study design, methods and clinical settings, comparison of risk with other populations may be helpful and a limitation of our study is that there was no direct comparator group. Consideration was given to calculating a Standard Mortality Ratio (SMR), i.e. the number of observed deaths in the IMMP cohort divided by the number of expected deaths in the age/sex-matched New Zealand population. However, New Zealand national mortality statistics available for the general population are stratified by age and sex, but not by bodyweight or BMI.[10] Previous research has reported a mean BMI of 26 in the general New Zealand adult population over 15 years of age,[15] whereas BMI data from a subgroup of patients in the IMMP sibutramine cohort indicated that our study population was obese, with a mean BMI of 34. Therefore, the New Zealand general population was not considered an appropriate comparator group for performing SMRs in this study.

It may be useful to compare the risk of death observed in the IMMP study with published risks in other overweight/obese general populations. Calle et al.[16] performed a prospective cohort study of BMI and mortality in more than 1 million adults in the US. The reported risk of death from all causes (in otherwise healthy overweight subjects who had never smoked) ranged from 1007 per 100 000 person-years for those with a BMI of 25–26.4, to 2065 per 100 000 for those with a BMI over 40. These risks are higher than those calculated for the IMMP study population, which translate to approximately 130 deaths per 100 000 person-treatment-years. Differences in levels of overweight/obesity may not explain the higher mortality in the American cohort as the IMMP cohort was also an obese population. There may be many other potential explanations for the lower mortality rate in the IMMP cohort, including the possibility that sibutramine lowers the risk of death in an overweight/obese general population.

Earlier in this IMMP study, a potential signal of long QT associated with sibutramine was identified[7] and there was a concern that this later record linkage study may have identified cases of sudden cardiac death or unexplained death, perhaps due to arrhythmias. It is reassuring to observe that this has not been the case. It appears that although approximately 6 per 1000 sibutramine patients experienced palpitations, the incidence of non-fatal arrhythmias was low. However, cardiac arrhythmias are not always documented and it remains possible that sibutramine prolongs the QT interval.[17] Clinically significant events such as torsade de pointes and/or cardiac arrest may only occur in those already at risk, for example those with congenital long QT syndrome[7] or taking other medicines that prolong the QT interval.

Four patients in the IMMP cohort died from cardiovascular causes, including myocardial in-

farction and stroke. Three of these deaths (two cases of stroke and one myocardial infarction) may have been associated with sibutramine treatment, as has been reported in other published cases.[18] However, the presence of confounding factors complicates assessment. Two of the patients in this IMMP cohort who died from cardiovascular causes had pre-existing hypertension, which is a risk factor for stroke and myocardial infarction. Sibutramine is known to increase blood pressure and heart rate,[19] and although there is some debate as to the magnitude of these effects[8] it is possible that the hypertensive effects of sibutramine added to the pre-existing risk in these patients. It would therefore seem appropriate not to prescribe sibutramine to patients with known hypertension, tachycardia or previous cardiovascular disease.

Conclusions

This study quantifies the cardiovascular risks of sibutramine in a general population in 'real-life' postmarketing use. The results show that the risk of death from a cardiovascular event in this population was lower than has been reported in other overweight/obese populations. As the current obesity epidemic shows no sign of waning and sibutramine continues to be widely available in many countries, it is important for prescribers and patients to have appropriate data on which to make informed clinical decisions.

Acknowledgements

During the time this study was conducted, the IMMP received funding from Medsafe, the medicines regulatory authority at the New Zealand Ministry of Health. Unconditional donations/grants have also been received from pharmaceutical companies, including Abbott Laboratories who are the New Zealand sponsor for sibutramine (Reductil®) and who provided an unconditional donation to the IMMP during the 3 years of data collection for this study.

None of the funding sources have had a role in the design, conduct, analysis or interpretation of the results of this study, nor have they been involved in the writing of this report.

None of the authors have any conflicts of interest to declare. All authors had full access to all of the data in the study and we take responsibility for the integrity of the data and the accuracy of the data analysis.

We are very grateful to Elizabeth Watson at the IMMP for her help in data preparation. We also thank Jim Slattery, biostatistician, for his input to this work and for reviewing early drafts of the manuscript.

The IMMP is a long-standing national medicines surveillance programme and its processes and practices have been approved by the New Zealand Privacy Commissioner. This study was carried out under the existing and ongoing IMMP ethical approval granted by the Otago Ethics Committee (reference OTA/04/32/CPD).

References

1. European Medicines Agency. European Medicines Agency recommends suspension of marketing authorizations for sibutramine. 21 January 2010 [press release; online]. Available from URL: http://www.ema.europa.eu/pdfs/human/referral/sibutramine/3940810en.pdf [Accessed 2010 May 11]
2. US Food and Drug Administration. Meridia (sibutramine hydrochloride): follow-up to an early communication about an ongoing safety review. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm198221.htm [Accessed 2010 May 19]
3. Torp-Pedersen C, Caterson I, Coutinho W, et al. Cardiovascular responses to weight management and sibutramine in high-risk subjects: an analysis from the SCOUT trial. Eur Heart J 2007; 28: 2915-23
4. Thirty-four deaths in sibutramine patients. Scrip 2002; 2730: 23
5. Advisory. Health Canada reports back to public on safety profile of Meridia (sibutramine). Ottawa (ON): Health Canada, 2003 Feb 28 [online]. Available from URL: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2003/2003_07-eng.php [Accessed 2010 May 19]
6. Harrison-Woolrych ML, Coulter DM. PEM in New Zealand. In: Mann R, Andrews EB, editors. Pharmacovigilance. 2nd edition. Chichester: John Wiley and Sons, 2007: 317-32
7. Harrison-Woolrych ML, Clark DWJ, Hill GR, et al. QT interval prolongation associated with sibutramine. Br J Clin Pharmacol 2006; 61 (4): 464-9
8. Williams G. Withdrawal of sibutramine in Europe. BMJ 2010; 340: c824
9. Kunac DL, Harrison-Woolrych ML, Tatley MV. Pharmacovigilance in New Zealand: the role of the New Zealand Pharmacovigilance Centre in facilitating safer medicines use. NZ Med J 2008; 121; 1281: 76-89 [online]. Available from URL: http://www.nzma.org.nz/journal/121-1283/3286 [Accessed 2010 May 11]
10. NZ Ministry of Health. Data and statistics: mortality collection (MORT) [online]. Available from URL: http://www.moh.govt.nz/moh.nsf/indexmh/dataandstatistics-collections-mortality [Accessed 2010 May 11]
11. Hill G, Harrison-Woolrych ML, Ashton J. Sibutramine utilisation in New Zealand: an analysis of prescription data by the Intensive Medicines Monitoring Programme. Pharmacoepidemiol Drug Saf 2007; 16: 1217-26
12. Ajani UA, Lotufo PA, Gaziano JM. Body mass index and mortality among US male physicians. Ann Epidemiol 2004; 14: 731-9

13. James WP, Astrup A, Finer N, et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Lancet 2000; 356: 2119-25
14. Abbott Laboratories (NZ) Ltd. New Zealand datasheet for Reductil [online]. Available from URL: http://www.medsafe.govt.nz/profs/Datasheet/r/Reductilcap.pdf [Accessed 2010 May 19]
15. Russell DG, Wilson NC, Parnell WR, et al. NZ food: NZ people. Key results of the 1997 National Nutrition Survey. Wellington: Ministry of Health, 1999 [online]. Available from URL: http://www.moh.govt.nz/moh.nsf/pagesmh/852 [Accessed 2010 May 11]
16. Calle EE, Thun MJ, Petrelli JM, et al. Body mass index and mortality in a prospective cohort study of US adults. N Engl J Med 1999; 341 (15): 1097-105
17. Ernest D, Gershenzon A, Corallo CE, et al. Sibutramine-associated QT interval prolongation and cardiac arrest. Ann Pharmacother 2008; 42: 1514-7
18. Eroglu E, Gemici G, Bayrak F, et al. Acute myocardial infarction in a 24 year-old man possibly associated with sibutramine use. Int J Cardiol 2009; 137: e43-5
19. von Haehling S, Lainscak M, Anker SD. Sibutramine in cardiovascular disease: is SCOUT the new STORM on the horizon? Eur Heart J 2007; 28: 2830-1

Correspondence: Dr *Mira Harrison-Woolrych*, Director, Intensive Medicines Monitoring Programme, Department of Preventive and Social Medicine, University of Otago, P.O. Box 913, Dunedin 9054, New Zealand.
E-mail: mira.harrison-woolrych@otago.ac.nz