Medicines Adverse Reactions Committee

Meeting date	**13 March 2013**	Agenda Item	3.2.1
Title	**Varenicline Tartrate (Champix) — IMMP Study Report Revised**		
Advisor(s)	[redacted]	Paper type	For advice

Active constituents	**Medicines**	**Sponsors**
Varenicline Tartrate	Champix	Pfizer

Funding	PHARMAC funded since October 2010
Previous MARC meetings	151st Meeting — 13 September 2012 Varenicline tartrate IMMP study report 147th Meeting — 8 September 2011 Varenicline & cardiovascular events 140th Meeting — 3 December 2009 Monitoring of varenicline (Champix) 137th Meeting — 12 March 2009 Intensive monitoring of varenicline tartrate (Champix) 133rd Meeting — 20 March 2008 Emerging safety issues with varenicline – early IMMP report
International Action	N/A
Prescriber Update	1. IMMP Update: Varenicline (Champix) monitoring. March 2012 2. The use of varenicline (Champix) in NZ: Key findings from IMMP study. September 2010 3. Psychiatric reactions with varenicline: interim results from intensive monitoring in New Zealand. May 2009
Schedule	Prescription medicine
Usage data	Included in this report
Advice sought	**The Committee is asked to advise whether:** • any regulatory action is recommended • if changes to the medicine data sheet are warranted • any communication is required.

1.0 PURPOSE OF REPORT

Varenicline tartrate (Champix) was approved for use in New Zealand in March 2007 and placed on the Intensive Medicines Monitoring Programme (IMMP) in that same year.

The IMMP study report of the data collected for the first three years since varenicline monitoring was started in 2007 was submitted to Medsafe on 30 June 2012. The Medicines Adverse Reaction Committee (MARC) reviewed this report and identified a number of issues that needed to be addressed before a robust assessment of the safety profile of varenicline in New Zealand could be made. The MARC recommended that an updated report be provided to Medsafe.

A revised IMMP study report along with new Annexes 3–5 was submitted to Medsafe on 27 November 2012 (Annex 1, 2, 3 and 4). IMMP report Annex 6 was submitted to Medsafe on 17 December 2012 (Annex 5). IMMP is currently revising Annex 4 and once completed this will be submitted to Medsafe (Annex 6). In addition, a revised IMMP report containing a revised Table 4.18 was submitted to Medsafe on 26 January 2013.

The purpose of this report is for the MARC to review the revised IMMP study report for varenicline and determine whether any actions are necessary as a result of this report.

2.0 BACKGROUND

2.1 Varenicline Pharmacology and Efficacy

Varenicline is a partial α4β2 nicotinic acetylcholine receptor agonist (1). Varenicline binds with high affinity and selectivity to produce an effect sufficient to alleviate symptoms of craving and withdrawal, while simultaneously resulting in blockade of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (1). The elimination half-life of varenicline is approximately 24 hours (individual range 10–58 hours) (1).

The efficacy of varenicline has recently been well described in a Cochrane review published in 2012 (2). Varenicline at standard dose increased the chances of successful long-term smoking cessation between two- and threefold compared with pharmacologically unassisted quit attempts (2). More participants quit successfully with varenicline than with bupropion (2).

2.2 Previous Regulatory Action in New Zealand

In March 2008, the MARC was notified that psychiatric reactions were emerging as a possible safety issue with varenicline. At that time, the data sheet had recently been updated to include information about psychiatric adverse events and update the precautions section.

In March 2009, the MARC was presented with an overview of the interim IMMP results from the first year of the varenicline study. At that time, the most common adverse effects reported were psychiatric events, including depression, suicidal ideation, sleep disorders, anxiety disorders and withdrawal symptoms. The MARC recommended that an article be published in *Prescriber Update* describing the psychiatric adverse events that have been reported in association with varenicline use and reminding prescribers to continue reporting adverse drug reactions. This *Prescriber Update* article was published in May 2009 (3).

In December 2009, the MARC reviewed the IMMP report following completion of the first year of follow up of the IMMP cohort. Medsafe also provided an update on the varenicline

safety profile, including a summary of the latest Periodic Safety Update Report (PSUR) and interim results from a UK based Prescription Event Monitoring (PEM) study.

Psychiatric events were the most common adverse effects reported particularly depression and sleep disturbance. The MARC noted that the majority of these psychiatric adverse effects are now listed in the New Zealand varenicline data sheet. The MARC agreed that no regulatory action was required at this time and noted that Medsafe will continue to monitor and evaluate international regulatory activity and safety-related data as it arises and would report back to the MARC as necessary.

In December 2010, an article was published in *Prescriber Update* reminding prescribers about the recommended course of treatment. This followed an IMMP finding that patients were regularly not receiving the full recommended 12 week course (4).

In September 2011, the MARC reviewed varenicline and cardiovascular events and were asked to to advise whether a causal association between varenicline treatment and cardiovascular events had been demonstrated and if any regulatory action was recommended. The MARC considered that although cardiovascular related safety concerns have been raised in association with varenicline, a causal relationship has yet to be demonstrated. The MARC agreed that this information does not alter the benefit-risk balance for varenicline, which remains positive. The MARC recommended that the New Zealand varenicline data sheet be updated to include information about reports of cardiovascular related adverse events associated with the use of varenicline. The data sheet was updated as recommended by the MARC.

A *Prescriber Update* article was published in March 2012 with an update on the interim findings from the IMMP study to date (5).

The IMMP study report was submitted to Medsafe on 30 June 2012. This report included a final analysis of the data collected since varenicline monitoring was started in 2007. The MARC reviewed this IMMP study report at the 151st meeting in September 2012. The MARC identified a number of issues that need to be addressed before a robust assessment of the safety profile of varenicline in New Zealand could be made. The MARC recommended that the updated report be provided to Medsafe. The MARC recommended that:

- the varenicline IMMP study report has a number of deficiencies and does not represent a "final" report, and recommended that the IMMP be requested to provide further information
- data from the fourth year of the study and an analysis of these data be provided
- that a re-analysis of the IMMP data be undertaken, removing events that occurred between one month and six months after stopping varenicline ('post-medicine' events).
- full case details be provided relating to the section of the report regarding psychiatric events
- the section of the report regarding suicide and suicidal ideation be reanalysed, taking into account the limitations of the data, confounding factors, and the nature of the population included in the study
- the results of the CAT study requested by the FDA be reviewed when they are published
- the lack of discussion in the IMMP report regarding the limitations of the data be addressed
- the lack of discussion in the IMMP report regarding possible confounding factors and comparison with other sources be addressed
- an overall summary of all events reported in the IMMP study, along with line listings of all cases be provided

- the IMMP report on varenicline be brought back to the MARC when sufficient information and clarification had been provided to enable a robust review of the conclusions stated by the IMMP and whether any regulatory action is required.

A revised IMMP study report was submitted to Medsafe on 27 November 2012. This contained numerous revisions and new Annexes 3–5. In addition to this, a new Annex 6 was submitted on to Medsafe on 17 December 2012 containing updated safety tables separating adverse events into on-medicine and off-medicine. IMMP has notified Medsafe that an updated Annex 4 is in preparation and will be submitted to Medsafe once completed.

In addition to the above regulatory action, Medsafe routinely reviews and assesses the Periodic Safety Update Reports (PSURs) for Champix and any completed safety studies.

3.0 IMMP STUDY REPORT

3.1 Cohort Data

Community and hospital pharmacies were asked for dispensing data every four months. Dispensing data from community and hospital pharmacies were collected and entered for patients who were dispensed varenicline for four years (from 1 April 2007 to 31 March 2011). During the four year period, **23,721** patients in New Zealand were dispensed varenicline (Table 1).

Table 1: Patients dispensed varenicline and follow-up data from the IMMP study

	Number Dispensed (% of Total)	Valid Questionnaires Returned (% of Dispensed)
First Year (Apr 2007 to Mar 2008)	3,425 (14.4%)	1,289 (37.6%)
Second Year (Apr 2008 to Mar 2009)	5,117 (21.6%)	1,740 (34.0%)
Third Year (Apr 2009 to Mar 2010)	4,297 (18.1%)	1,799 (41.9%)
Fourth Year (Apr 2010 to Mar 2011)	10,882 (45.9%)	Not provided
Total	**23,721 (100%)**	**4,828**

Follow-up questionnaires were sent to all identifiable patients with identifiable prescribers. Patient follow-up was presented in the IMMP report for only the first three years of the study (ie, 1 April 2007 to 31 March 2010). A total of 4,828 questionnaires relating to **4,783** patients were returned (Table 1).

Following completion of the follow-up questionnaire, data linkage of the patient's NHI number to the national morbidity and mortality datasets identified any death or adverse events which resulted in hospital admission since the patient started on the medicine. Data linkage was also undertaken for patients who had not returned a follow-up questionnaire.

The IMMP also identifies adverse events from spontaneous reports that were sent to the Centre for Adverse Reaction Monitoring (CARM) and from duplicate prescriptions.

Medsafe comment
The increase seen in the fourth year is likely a direct result PHARMAC funding varenicline. PHARMAC funding began in October 2010, six months in to the final year.

The number of valid questionnaires returned was less than 40 % which severely limits the conclusions that can be drawn from this study.

The follow-up data did not include any patients who were dispensed the medicine in the fourth year of the study (10,882 patients). Therefore, no patient follow-up was analysed for those who were dispensed varenicline after the medicine was funded.

Medsafe and the MARC have requested the data from the fourth year of the IMMP study. However, to date Medsafe has not received this data and the IMMP are yet to commit to providing this data.

No information was provided in the report to validate the data linkage methodology. Whilst all hospital admissions were recorded and linked to patients in the IMMP study, this does not include private hospitals. It is not clear how patients were determined to be 'on-medicine' at the time of hospital admission.

3.2 Dispensing Analysis

Patient age, sex and ethnicity was analysed for all patients dispensed varenicline (23,721 patients) during the first four year period of the IMMP study. Treatment duration analysis was performed on the first three years dispensing data (12,839 patients) only.

3.2.1 Patient Age

Patient age was identified for 99.2 % of the patients who were dispensed varenicline in the four year cohort. The mean and median ages were 47.2 years and 47 years respectively with a range of 14 to 91 years (Table 2). There were no differences between the men and women's median age in the cohort.

Table 2: Age of varenicline patients at time of first prescriptions during the four year period

Age Group (years)	Number	% of Cohort
10 - 19	107	0.5
20 - 29	1801	7.6
30 - 39	4556	19.2
40 - 49	6918	29.2
50 - 59	6142	25.9
60 - 69	3335	14.1
70 - 79	608	2.6
80 plus	56	0.2
Unknown age	198	0.8
Total	**23721**	**100**

There were 22 patients (0.09 %) under 18 years of age who were dispensed varenicline during the four year period.

Medsafe comment
The New Zealand varenicline data sheet does not recommend use in patients under 18 years of age as the safety and effectiveness has not been established (1) (Annex 7).

Of note, Pfizer are currently undertaking a twelve-week, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study with follow-up evaluating the safety and efficacy of varenicline for smoking cessation in healthy adolescent smokers that is due for completion in 2014.

During the four years that dispensing data was collected, 664 patients (2.8 %) were 70 years or older.

3.2.2 Patient Sex

Patient sex was identified for 99.9 % of the patients who were dispensed varenicline during the four year period. Slightly more females were dispensed varenicline (53.3 %) compared to males (46.7 %).

3.2.3 Patient Ethnicity

Patient ethnicity was available for 89 % of the patients who were dispensed varenicline (Table 3). The majority of patients who were dispensed varenicline considered themselves European (84.4 %). This is slightly more than the figure from the 2006 Census where 64.7 % of the population identified themselves as European. Maori, Pacific Island, Asian and other ethnicities were all lower proportionally than expected from the 2006 Census.

Table 3: Ethnicity of patients in varenicline cohort during the four year period

Ethnicity	Number	Per cent (%) cohort	Per cent (%) NZ Population[1]
European	17869	84.4	67.6
Maori	2622	12.4	14.6
Pacific Island	258	1.2	6.9
Asian	291	1.4	9.2
Other	133	0.6	12.1
Total	**21173**	**100**	**110.4[2]**

[1] The figures in this column have been derived from the Census 2006 statistics for the population of NZ (www.stats.govt.nz/Census/2006CensusHomePage).
[2] This total is greater than 100 % as in the Census patients can chose to identify with more than one ethnic group.

Medsafe comment
For the first three years of the IMMP study, varenicline was not a funded medicine. It would have been interesting to see the dispensing data separated into pre-varenicline funding and post-varenicline funding.

To determine if there was a difference in use between ethnic groups, the percentage of each ethnic group that smoked is needed.

3.2.4 Treatment Duration

The recommended initial dose when starting varenicline is 0.5 mg once daily for days 1–3, 0.5 mg twice daily for days 4–7 and 1 mg twice daily from day eight until the end of treatment. The New Zealand data sheet states that the patient should be treated with varenicline for 12 weeks and recommends an additional course of 12 weeks for those who have been successful. The sponsor markets a starter pack that includes the first 14 days of treatment. In the first three years of the study, 11,025 patients (86 %) were dispensed a starter pack.

To determine the dosage of varenicline following initiation of treatment, the first prescription from each course was excluded. The larger majority of treatment excluding the initial prescription was for a daily total dose of 2 mg (95 % of prescriptions). The remaining prescriptions were for a daily dose of 1 mg (5 % of prescriptions).

Duration of treatment was analysed only for all patients who were dispensed varenicline in the first three years of the study and for the first course of continuous treatment only.

In the first three years of the study, 11,710 patients (91 % of patients) were dispensed varenicline for 12 weeks or less. Of these patients, only 386 were dispensed 12 weeks of treatment. The most common duration of treatment in the first three years was two weeks with 4,536 patients (35 % of patients) dispensed varenicline (Figure 1). This was followed by six weeks with 2,921 patients (23 % patients) dispensed varenicline. There were 89 patients (0.7 %) who were dispensed more than 24 weeks of varenicline in the first three years of the IMMP study. Of the 89 patients who were dispensed more than 24 weeks, 10 patients were dispensed over 300 days of varenicline.

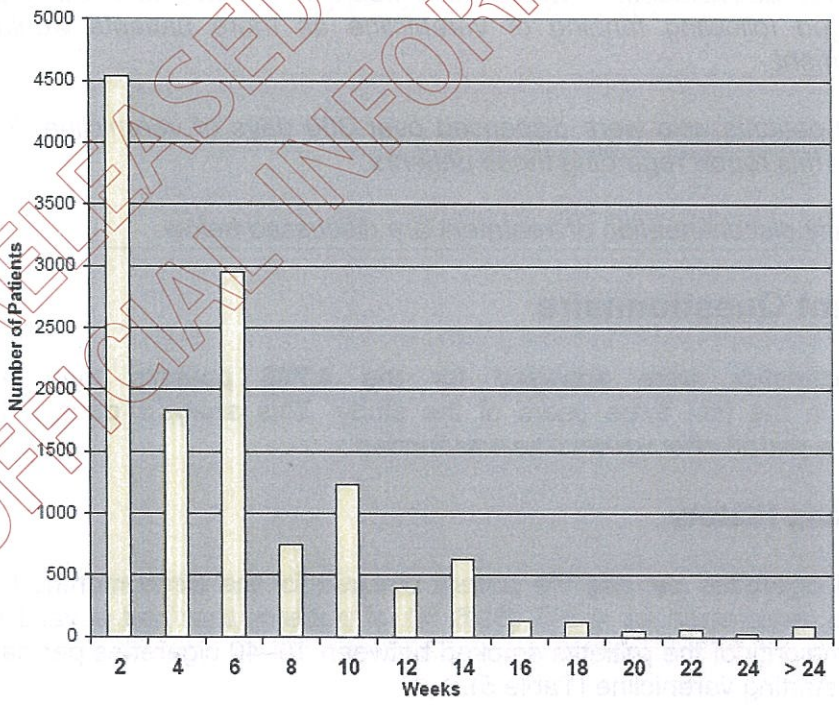


Figure 1: Duration of dispensed varenicline in first three years of the study (From IMMP report)

The majority of patients in the first three years of the study had one course of varenicline treatment (68.9 %) (Table 4). This was followed by patients who were dispensed two courses of varenicline (21.5 %). There were 39 patients who were dispensed six or seven courses of varenicline in the first three years of the study.

Table 4: Number of courses dispensed to patients in the first three years of the study

Course	Patients	% of cohort
1	8851	68.9
2	2759	21.5
3	852	6.6
4	257	2.0
5	81	0.6
6	35	0.3
7	4	0
Total Patients	**12839**	**100**

Medsafe comment
Interestingly, the majority of patients in the first three years (88.2 %) were dispensed less than the recommended 12 week course of varenicline. A Prescriber Update article was published in September 2010 following interim analysis to remind prescribers that the varenicline data sheet advises a 12 week course and that failure to complete the course may have implications for the effectiveness of smoking cessation (6).

No dispensing data was analysed for duration of varenicline treatment for the fourth year of the IMMP study. The MARC and Medsafe have previously requested data from the fourth year of the study be included. It would have been informative to know if the treatment duration changed following funding of varenicline as more patients would likely have continued treatment.

There were 10 patients who were dispensed over 300 days of varenicline. No information was provided in this report regarding those patients.

Reasons for early discontinuation of treatment are discussed below.

3.3 Patient Questionnaire

Patient characteristics were analysed for the **4,783** patients that returned valid questionnaires in the first three years of the study. This analysis does not include any patients from the period after varenicline was funded.

3.3.1 Smoking History

The number of cigarettes per day the patient smoked for the three months before starting varenicline was determined for 4,297 (89.8 %) of patients that had a valid questionnaire returned. The majority of the patients smoked between 10–40 cigarettes per day in the three months before starting varenicline (Table 5).

Table 5: Questionnaire smoking history of patients in the first three years of the study

Cigarettes per day	Number	% of 4550
< 10	341	7.5
10 - 20	2348	51.6
21 - 40	1383	30.4
> 40	97	2.1
Other	128	2.8
Unknown *	253	5.6

* Unknown means unknown to the doctor responding to the questionnaire

3.3.2 Previous Smoking Cessation Treatment

Whether the patient had attempted to quit smoking or not was answered for 4,528 (95 %) patients. The majority of patients (3307; 73.0 %) had previously tried to quit. Patients who had not previously attempted to quit smoking accounted for 20.2 % of patients, with the remaining 6.8 % unknown. Previous attempts at smoking cessation included no medication, nicotine replacement and bupropion (Table 6).

Table 6: Questionnaire method of smoking cessation prior to varenicline in the first three years

Previous Treatment	Number	Proportion of 3,307 patients (%)
No Medication	684	21
Nicotine Replacement Therapy	1,464	44
Bupropion (Zyban®)	309	9
Other	415	12
Method not reported	1,036	31
Total	3,307	100

Of the patients that reported a previous attempt to quit smoking, 1743 patients (76.75 %) had used one method, 458 patients (20.17 %) had used two methods, 67 patients (2.95 %) and three patients (0.13 %) had used four or more methods.

Medsafe comment
The total number in Table 6 is incorrect. The total number of previous treatments tried should be 3908 (by 3307 patients).

The number of patients that had not previously tried to quit smoking (913 patients) would not be aware of withdrawal symptoms. The efficacy is likely to be lower in patients with previous unsuccessful attempts at smoking cessation.

3.3.3 Medical History

Past medical history was determined for the patients receiving varenicline. The questionnaire specifically enquired whether the patient had a medical history of psychiatric illness, convulsions/seizures, ischaemic heart disease or any other significant history.

Of those that responded to the questions:

- 806 patients (17.8 % of responders) had a history of psychiatric illness
- 35 patients (0.8 % of responders) had a history of convulsions/seizures
- 264 patients (6 % of responders) had a history of ischaemic heart disease
- 1032 patients had some other significant history.

Medsafe comment
The IMMP study report did not specify what the other significant medical histories were that were included in the questionnaire.

3.3.4 Premature Cessation of Treatment

The questionnaire asked whether the patient completed 12 weeks of varenicline treatment. Of the valid questionnaires, the question was completed by the doctor for 4,558 patients. There were 1536 patients (35 %) who were reported to not have completed 12 weeks of treatment. There were 1270 patients who indicated a reason for not completing the 12 weeks of treatment.

The main reasons for prematurely stopping varenicline treatment were an adverse reaction, cost and poor compliance (Table 7).

Table 7: Premature cessation of treatment in the first three years of the study from the questionnaires

Reason	Frequency	% of 1270 patients
Adverse reaction	498	39.2
Too expensive	249	19.6
Poor compliance	217	17.1
Inadequate therapeutic response	103	8.1
No longer necessary	117	9.2
Reason unknown to Doctor	113	8.9
Reason unrelated to drug	62	4.9
Patient died[1]	6	0.5
Totals[2]	1365*	107.5*

[1] This group of patients includes all patients identified as having died as at 31 March 2012, including deaths unrelated to varenicline treatment.
[2] Figures are >100% total as 101 patients had more than one reason for stopping treatment.

The IMMP study also examined the causes of premature cessation of varenicline treatment in the first three years of the study from the questionnaires, spontaneous reports and duplicate prescriptions.

The reason for prematurely stopping treatment was identified in 1595 patients from the first three years of the study (12.4 % of patients). This is 59 extra patients than determined from the questionnaires alone. In the 1595 patients, a total of 1696 reasons for stopping treatment were recorded. Of the 1696 reasons, the main reasons for prematurely stopping varenicline treatment were an adverse reaction, cost and poor compliance (Table 8).

Table 8: Premature cessation of treatment in the first three years of the study

Reason	Frequency	% of 1595 patients
Adverse reaction	655	41.1
Too expensive	292	18.3
Poor compliance	243	15.2
Inadequate therapeutic response	141	8.8
No longer necessary	126	7.9
Reason unknown to Doctor	122	7.6
Reason unrelated to drug	64	4
Patient died[1]	53	3.3
Totals[2]	**1696**	**106.2**

Medsafe comment
It should be noted that whilst the percentage of patients stopping due to an adverse reaction appears high at 41 %, only 13 % of the three year cohort was included in this analysis. It is unknown if those who didn't respond had different reasons for stopping.

It would have been interesting to see what the reasons for premature cessation of treatment were once varenicline was funded as cost was a significant factor in patients stopping.

The adverse reactions leading to cessation of varenicline treatment were not detailed.

3.3.5 Effectiveness of Smoking Cessation

The effectiveness of varenicline was determined for 4521 patients during the first three years of the study who had a valid questionnaire returned. Smoking cessation was successful in 28.7 % of patients, unsuccessful in 37.8 % of patients and unknown in the remaining 33.5 % of patients.

Medsafe comment
The time at which smoking cessation was determined (ie, one week or six months) was not included. It would have been of interest to determine if treatment with varenicline was more or less effective in those who had previously tried to quit smoking.

The New Zealand data sheet for varenicline indicates that in clinical trials, the four week continuous quit rate for varenicline was approximately 40 % compared with 18 % for placebo and the long term quit rate at 52 weeks for varenicline was approximately 25 % compared with 10–13 % for placebo (1).

There is not enough information provided in the IMMP study to draw any conclusions from this data as smoking status was unknown in a third of the patients who had a valid questionnaire returned. It is also important to note that the majority of the questionnaires were completed by the patients' GP and not the patients.

3.4 Adverse Events

In the IMMP analysis, adverse events are defined as following:

- on-medicine; events occurring whilst the patient is taking varenicline
- off-medicine; events occurring in the month after stopping varenicline
- post-medicine; events that occurred between one month and six months after stopping varenicline.

In the tables displayed below, the responder population refers to those patients that returned a valid questionnaire in the first three years of the IMMP study.

Adverse events that occurred in the first three years of the IMMP study were examined. From the cohort of 12,839, there were a total of **5165** events from **3078** reports. Of the 5165 events, **2663** events (51.6 %) occurred in patients taking varenicline (Table 9).

Table 9: Adverse events for patients in the first three years of the IMMP study

Event category	Events
On medicine	2,663
Off medicine	481
Post-medicine	2,021
Total	5,165

Adverse events identified for the first three years of the study were classified by system organ class (SOC) (Table 10).

Table 10: IMMP adverse events by IMMP SOC in the first three years of the study (Revised IMMP Table 4.18)

	On medicine events		Off medicine events		Post-medicine events		Total	
Group	Number	%	Number	%	Number	%	Number	%
Alimentary	708	26.6	69	14.3	221	10.9	998	19.3
Psychiatric	764	28.7	47	9.8	158	7.8	969	18.8
Respiratory	160	6.0	69	14.3	251	12.4	480	9.3
Circulatory	152	5.7	44	9.1	212	10.5	408	7.9
Musculoskeletal	121	4.5	28	5.8	202	10.0	351	6.8
Accidents	90	3.4	50	10.4	198	9.8	338	6.5
Urogenital	85	3.2	34	7.1	140	6.9	259	5.0
Neurological	102	3.8	21	4.4	72	3.6	195	3.8
ENT	64	2.4	21	4.4	98	4.9	183	3.5
Skin	72	2.7	17	3.5	88	4.4	177	3.4
Endocrine/Metabolic	86	3.2	10	2.1	62	3.1	158	3.1
Infections	37	1.4	16	3.3	81	4.0	134	2.6
Neoplasms	40	1.5	21	4.4	72	3.6	133	2.6
Eyes	36	1.4	3	0.6	34	1.7	73	1.4
Unclassified	46	1.7	1	0.2	3	0.1	50	1.0
Died	5	0.2	8	1.7	34	1.7	47	0.9
Autonomic	38	1.4	1	0.2	7	0.3	46	0.9
Haematological	10	0.4	9	1.9	25	1.2	44	0.9
Hepatobiliary	9	0.3	1	0.2	30	1.5	40	0.8
Surgery	10	0.4	5	1.0	22	1.1	37	0.7
Immunological	3	0.1	5	1.0	11	0.5	19	0.4
Pregnancy Exposure	14	0.5	1	0.2	0	–	15	0.3
Associations	11	0.4	0	–	0	–	11	0.2
Total Events	2,663	100.0	481	100.0	2,021	100.0	5,165	100.0

Medsafe comment
The adverse events used in the IMMP study were classified according to SOC using the IMMP events dictionary. Although based on WHO-ART, the IMMP events dictionary has not undergone peer review to ensure the classification represents current medical practice as is the case for WHO-ART or MedDRA. This also means that care must be taken when comparing the results of this study with other studies using different event dictionaries.

Of the 3,078 adverse event reports in the study, the majority of the reports were identified from the questionnaire (59.2 %). This data included all reports with on-medicine, off-medicine and post-medicine events. The remaining reports were identified from NZHIS hospital events (33.6 %), duplicate prescriptions (3.4 %), spontaneous reports (2.9 %), industry (1.0 %) and pharmacists (0.1 %).

A summary of all events reports identified by NZHIS hospital data linkage is attached in Annex 5 of the IMMP report.

Medsafe comment
The IMMP hospital data linkage was not validated in this report. Unsurprisingly given the lack of information about these reports, the majority of the reports (~95 %) identified by this method were found to be of unlikely or unclassifiable causality in relation to varenicline.

The top ten events reported while the patient was taking varenicline were determined for the first three years of the study (Table 11). All events were included whether a causal relational was established or not. The most common adverse event reported was nausea.

Table 11: Top ten adverse events including both causal and coincidental events in the first three years of the IMMP study (From Annex 6)

	Medsafe cohort n= 12,839			
Event	Number on med events	Rate per 1000 pts	Number off-med events	Rate per 1000 pts
Nausea	358	27.9	7	0.5
Accidents[1]	90	7.0	50	3.9
Depression	98	7.6	8	0.6
Insomnia	83	6.5	2	0.2
Headache	62	4.8	4	0.3
Neoplasms[1]	40	3.1	21	1.6
Dreams	59	4.6	0	0.0
Paroniria	59	4.6	0	0.0
Fatigue	48	3.7	7	0.5
Vomiting	50	3.9	3	0.2

[1] The event terms 'accidents' and 'neoplasms' include within each print code sub-groups of different accidents/neoplasms

Medsafe comment
All the top ten events are listed in the New Zealand data sheet with the exception of accidents, neoplasms and 'paroniria' (nightmare). 'Abnormal dreams' is listed in the New Zealand data sheet. It is important to note that all events were included whether a causal relationship was established or not.

The adverse events that were identified in the top ten clinical groups were determined (Table 12). All events were included whether a causal relationship was established or not.

Table 12: Top ten clinical groups of adverse events including both causal and coincidental events in the first three years of the study (From Annex 6)

		Medsafe cohort n=12,839			
Clinical grouping / Event	Event	Number on-med events	Rate per 1000 pts	Number off-med events	Rate per 1000 pts
Nausea & vomiting	Anorexia	12	0.93	1	0.08
	Nausea	358	27.88	7	0.55
	Vomiting	50	3.89	3	0.23
	Sub-group total	420	32.71	11	0.86
Sleep disorders	Dreams	59	4.60	0	0.00
	Insomnia	83	6.46	2	0.16
	Insomnia worse	2	0.16	0	0.00
	Paroniria	59	4.60	0	0.00
	Sleep disturbance	46	3.58	2	0.16
	Sleep disturbance worse	1	0.08	0	0.00
	Somambulism	1	0.08	0	0.00
	Sub-group total	251	19.55	4	0.31
Depression and suicidality	Depression	98	7.63	8	0.62
	Depression worse	46	3.58	2	0.16
	Tearful	6	0.47	0	0.00
	Self injury worse	1	0.08	0	0.00
	Overdose	4	0.31	2	0.16
	Suicidal ideation	16	1.25	0	0.00
	Suicide	1	0.08	2	0.16
	Suicide attempt	1	0.08	2	0.16
	Motivation impaired	2	0.16	1	0.08
	Sub-group total	175	13.63	17	1.32
Accidents	Accidents	90	7.01	50	3.89
	Sub-group total	90	7.01	50	3.89
Anxiety & agitation	Emotional lability	6	0.47	1	0.08
	Anxiety	32	2.49	0	0.00
	Anxiety worse	9	0.70	1	0.08
	Restlessness	2	0.16	0	0.00
cont'd	Speech disorder	2	0.16	0	0.00
	Irritability	25	1.95	3	0.23
	Irritability worse	2	0.16	0	0.00
	Panic	9	0.70	0	0.00
	Panic worse	1	0.08	0	0.00
	Stress reaction	15	1.17	5	0.39
	Stress reaction worse	0	0.00	1	0.08
	Agitation	7	0.55	0	0.00
	Aggression	13	1.01	0	0.00
	Sub-group total	123	9.58	11	0.86

Headaches and migraine	Headache	62	4.83	4	0.31
	Migraine	7	0.55	2	0.16
	Migraine more frequent	2	0.16	0	0.00
	Migraine recurrence	1	0.08	1	0.08
	Sub-group total	72	5.61	7	0.55
Tiredness/fatigue	Exhaustion	2	0.16	0	0.00
	Fatigue	48	3.74	7	0.55
	Heavy feeling	1	0.08	0	0.00
	Weakness	1	0.08	0	0.00
	Somnolence	19	1.48	1	0.08
	Sub-group total	71	5.53	8	0.62
Respiratory infections	Flu-like illness	10	0.78	7	0.55
	Influenza	4	0.31	1	0.08
	Viral infection	4	0.31	1	0.08
	Pharyngitis	0	0.00	5	0.39
	URTI	22	1.71	12	0.93
	Respiratory infection	2	0.16	0	0.00
	Sub-group total	42	3.27	26	2.03
Gastro-oesophageal reflux	Chest pain (oesophageal)	2	0.16	2	0.16
	Heartburn	3	0.23	0	0.00
	Oesophagitis	0	0.00	1	0.08
	Reflux dyspepsia	21	1.64	2	0.16
	Abdominal pain upper	3	0.23	0	0.00
	Dyspepsia	12	0.93	1	0.08
	Dyspepsia worse	1	0.08	0	0.00
	Epigastric pain	6	0.47	1	0.08
	Gastric ulcer	0	0.00	1	0.08
	Gastritis	4	0.31	1	0.08
	GI bleeding	0	0.00	1	0.08
	Stools dark	1	0.08	0	0.00
	Sub-group total	53	4.13	10	0.78
Myocardial ischaemia	Angina	6	0.47	3	0.23
	Angina worse	2	0.16	0	0.00
	Coronary insufficiency worse	1	0.08	0	0.00
	Ischaemic heart disease	2	0.16	0	0.00
	Chest discomfort	1	0.08	0	0.00
	Chest heaviness	1	0.08	1	0.08
	Chest pain	16	1.25	6	0.47
	Chest pain worse	7	0.55	0	0.00
	Chest tightness	2	0.16	0	0.00
	Myocardial infarction	8	0.62	5	0.39
	Myocardial infarct worse	1	0.08	0	0.00
	Sub-group total	47	3.66	15	1.17

Medsafe comment
The adverse events classified in this table have been grouped by clinical group and not by SOC as is standard. The methodology for determining these grouping has not been stated. The groups do not correspond to validated groups as defined by MedDRA or WHO-ART. For example, in MedDRA there is no equivalent group for the IMMP gastro-oesophageal reflux group. The terms included in this IMMP group are spread throughout multiple HLGT groups in the gastrointestinal disorders SOC in MedDRA.

The top ten adverse events and the top ten clinical groups included all events and were not restricted to those events assessed as having causal relationship with varenicline. The majority of the top ten events are single events yet accidents and neoplasms include all subgroups.

Of top ten events identified in the IMMP report, the only individual adverse event not listed in the New Zealand data sheet is 'paroniria' (nightmare). 'Nightmare' should be included in the New Zealand data sheet.

3.4.1 Psychiatric Adverse Events

There were 765 psychiatric adverse events in patients on varenicline treatment identified for the first three years of the study (Table 13).

Table 13: Psychiatric events reported in the first three years of the IMMP study (From Annex 6)

Psychiatric system organ class		Medsafe cohort n=12,839			
Clinical sub-group	Event	Number on-med events	Rate per 1000 pts	Number off-med events	Rate per 1000 pts
Sleep disorders	Insomnia	83	6.46	2	0.16
	Insomnia worse	2	0.16	0	0.00
	Sleep disturbance	46	3.58	2	0.16
	Sleep disturbance worse	1	0.08	0	0.00
	Somambulism	1	0.08	0	0.00
	Dreams	59	4.60	0	0.00
	Paroniria	59	4.60	0	0.00
	Sub-group total	251	19.55	4	0.31
Tiredness events	Exhaustion	2	0.16	0	0.00
	Fatigue	48	3.74	7	0.55
	Somnolence	19	1.48	1	0.08
	Heavy feeling	1	0.08	0	0.00
	Malaise	16	1.25	1	0.08
	Weakness	1	0.08	0	0.00
	Sub-group total	87	6.78	9	0.70
Depression	Depression	98	7.63	8	0.62
	Depression worse	46	3.58	2	0.16
	Tearful	6	0.47	0	0.00
	Motivation impaired	2	0.16	1	0.08
	Sub-group total	152	11.84	11	0.86
Suicide & self harm	Suicide	1	0.08	2	0.16
	Suicide attempt	1	0.08	2	0.16
	Overdose	4	0.31	2	0.16
	Self injury worse	1	0.08	0	0.00
	Suicidal ideation	16	1.25	0	0.00
	Sub-group total	23	1.79	6	0.47
Mood disorders	Mood swings	20	1.56	0	0.00
	Emotional lability	6	0.47	1	0.08
	Mood elevation	3	0.23	0	0.00
	Mood altered	7	0.55	0	0.00

Psychiatric system organ class		Medsafe cohort n=12,839			
Clinical sub-group	Event	Number on-med events	Rate per 1000 pts	Number off-med events	Rate per 1000 pts
cont'd	Hypomania	2	0.16	0	0.00
	Sub-group total	38	2.96	1	0.08
Anxiety disorders	Anxiety	32	2.49	0	0.00
	Anxiety worse	9	0.70	1	0.08
	Irritability	25	1.95	3	0.23
	Irritability worse	2	0.16	0	0.00
	Panic	9	0.70	0	0.00
	Panic worse	1	0.08	0	0.00
	Stress reaction	15	1.17	5	0.39
	Stress reaction worse	0	0.00	1	0.08
	Restlessness	2	0.16	0	0.00
	Sub-group total	95	7.40	10	0.78
Aggressive reactions	Agitation	7	0.55	0	0.00
	Aggression	13	1.01	0	0.00
	Sub-group total	20	1.56	0	0.00
Cognitive changes	Depersonalisation	21	1.64	0	0.00
	Attitude change	1	0.08	0	0.00
	Behaviour abnormal	1	0.08	0	0.00
	Concentration impaired	16	1.25	2	0.16
	Function impaired	1	0.08	0	0.00
	Thinking abnormal	3	0.23	0	0.00
	Confusion	3	0.23	1	0.08
	Disorientation	1	0.08	0	0.00
	Sub-group total	47	3.66	3	0.23
Psychotic events	Hallucinations	4	0.31	0	0.00
	Psychosis	1	0.08	0	0.00
	Manic depressive psychosis	2	0.16	0	0.00
	Psychotic reaction	2	0.16	0	0.00
	Paranoia	5	0.39	0	0.00
	Sub-group total	14	1.09	0	0.00
Withdrawal symptoms	Withdrawal anxiety	2	0.16	0	0.00
	Withdrawal anxiety and depression	1	0.08	0	0.00
	Withdrawal depression	6	0.47	0	0.00
	Withdrawal symptoms	14	1.09	0	0.00
	Sub-group total	23	1.79	0	0.00
Alcohol/Substance abuse	Drug abuse worse	1	0.08	0	0.00
	Substance abuse worse	1	0.08	0	0.00
	Alcohol abuse	2	0.16	1	0.08
	Alcohol abuse worse	2	0.16	1	0.08
	Sub-group total	6	0.47	2	0.16
Other	Memory impairment	6	0.47	0	0.00
	Speech disorder	2	0.16	0	0.00
	Anorexia	1	0.08	0	0.00
	Sub-group total	9	0.70	0	0.00
Total		765	59.59	46	3.58

The most commonly reported psychiatric events were depression, insomnia, dreams, paroniria, fatigue, sleep disturbance, depression worse, anxiety, irritability, depersonalisation, mood swings, somnolence, malaise, suicidal ideation, concentration impaired, stress reaction and aggression.

Of the most reported adverse events in the IMMP psychiatric SOC, 'paroniria', 'sleep disturbance', 'depersonalisation', 'concentration impaired', and 'stress reaction' are not listed in the New Zealand data sheet. Although 'sleep disturbance' is not listed, 'sleep disorder' is listed. Difficulty concentrating is mentioned in the New Zealand data sheet as being associated with smoking cessation with or without treatment.

The clinical sub-groups used by IMMP do not correspond to validated groups as defined by MedDRA or WHO-ART. The IMMP sub-group of suicide and self-harm includes overdose. This is in contrast to the international accepted MedDRA terminology where overdose is in the injury, poisoning and procedural complications SOC; HLGT: medication errors; HLT: overdoses. In MedDRA, suicide and self-harm are in the psychiatric disorders SOC; HLGT: suicidal and self-injurious behaviours NEC; HLT: suicidal and self-injurious behaviour.

It is important to note that all events were included whether a causal relationship was established or not.

The numbers of adverse psychiatric events that occurred while on-medicine and off-medicine that were assessed as having a probable, possible or likely relationship with varenicline treatment are shown in Table 14. A description of the WHO causality assessment is included in Annex 8. Suicide/suicidal ideation were excluded from this table as these events are discussed later in the IMMP study report. Withdrawal events were also excluded as causality assessment was modified for these events.

Table 14: Causality assessment for psychiatric adverse events both <u>on-medicine</u> and <u>off-medicine</u> for the first three years of the IMMP study

Psychiatric system organ class		Number of events[1]	Events assessed as having causal relationship[2] with varenicline			
Clinical sub-group	Event		1	2	3	Total (%)
Sleep disorders	Insomnia	85		35	47	82 (96%)
	Insomnia worse	2			2	2 (100%)
	Sleep disturbance	48		16	31	47 (98%)
	Sleep disturbance worse	1			1	1 (100%)
	Somnambulism	1		1		1 (100%)
	Dreams	59		28	30	58 (98%)
	Paroniria	59		35	24	59 (100%)
	Sub-group total	255	0	115	135	250 (98%)
Tiredness events	Exhaustion	2			1	1 (50%)
	Fatigue	55		22	29	51 (93%)
	Somnolence	20		10	9	19 (95%)
	Heavy feeling	1		1		1 (100%)
	Malaise	17		8	7	15 (88%)
	Weakness	1			1	1 (100%)
	Sub-group total	96	0	41	47	88 (92%)
Depression	Depression	106	1	48	49	98 (92%)
	Depression worse	48		18	29	47 (98%)
	Tearful	6	1	3	2	6 (100%)
	Motivation impaired	3		2	1	3 (100%)
	Sub-group total	163	2	71	81	154 (94%)
Mood disorders	Mood swings	20		14	6	20 (100%)
	Emotional lability	7		5	2	7 (100%)
	Mood elevation	3			2	2 (67%)
	Mood altered	7		1	6	7 (100%)
	Hypomania	2			2	2 (100%)
	Sub-group total	39	0	20	18	38 (97%)
Anxiety disorders	Anxiety	32		15	17	32 (100%)
	Anxiety worse	10		5	3	8 (80%)
	Irritability	28		18	9	27 (96%)
	Irritability worse	2		1	1	2 (100%)
	Panic	9		4	5	9 (100%)
	Panic worse	1		1		1 (100%)
	Stress reaction	20		1	8	9 (45%)
	Stress reaction worse	1				0 (0%)
	Restlessness	2		1	1	2 (100%)
	Sub-group total	105	0	46	44	90 (86%)

Psychiatric system organ class		Number of events[1]	Events assessed as having causal relationship[2] with varenicline			
Clinical sub-group	Event		1	2	3	Total (%)
Aggressive reactions	Agitation	7		3	3	6 (86%)
	Aggression	13		10	3	13 (100%)
	Sub-group total	**20**	**0**	**13**	**6**	**19 (95%)**
Cognitive changes	Depersonalisation	21		13	8	21 (100%)
	Attitude change	1		1		1 (100%)
	Behaviour abnormal	1			1	1 (100%)
	Concentration impaired	18		10	6	16 (89%)
	Function impaired	1		1		1 (100%)
	Thinking abnormal	3		3		3 (100%)
	Confusion	4		2	1	3 (75%)
	Disorientation	1	1			1 (100%)
	Sub-group total	**50**	**1**	**30**	**16**	**47 (94%)**
Psychotic events	Hallucinations	4		2	2	4 (100%)
	Psychosis	1			1	1 (100%)
	Manic depressive psychosis	2			2	2 (100%)
	Psychotic reaction	2			1	1 (50%)
	Paranoia	5		4	1	5 (100%)
	Sub-group total	**14**	**0**	**6**	**7**	**13 (93%)**
Alcohol/Substance abuse	Drug abuse worse	1				0 (0%)
	Substance abuse worse	1				0 (0%)
	Alcohol abuse	3			1	1 (33%)
	Alcohol abuse worse	3			1	1 (33%)
	Sub-group total	**8**	**0**	**0**	**2**	**2 (25%)**
Other	Memory impairment	6		5	1	6 (100%)
	Speech disorder	2		2		2 (100%)
	Anorexia	1		1		1 (100%)
	Sub-group total	**9**	**0**	**8**	**1**	**9 (100%)**
Total		759	3	364	363	710 (94%)

[1] Includes all on-medicine and off-medicine events
[2] Causal relationship: 1=certain, 2=probable, 3=possible

Of the 759 adverse psychiatric events (both on-medicine and off-medicine) that were included in this analysis (suicide and withdrawal sub-group events were excluded), three (0.4 %) were assessed as certain, 350 (46.1 %) were assessed as probable and 357 (47.0 %) were assessed as possible (50.3 %).

Medsafe comment
Of note, the numbers in the totals are incorrectly added and should be as follows: 759, 3, 350, 357 and 710.

The causality assessment table is displayed in events and not cases (eg, the events depression and tearful assessed as having a certain causal relationship with varenicline are the same case).

The data sheet for varenicline currently contains a precaution regarding psychiatric symptoms and psychiatric adverse events from post-marketing experience (1). The data sheet also states that discontinuation of Champix was associated with an increase in irritability, urge to smoke, depression and/or insomnia in up to 3 % of patients. Patients and their families are advised to monitor for changes in behaviour or thinking, anxiety, psychosis, mood swings, agitation, aggression, depressed mood, suicidal ideation and suicidal behaviour.

Adverse events reported from the clinical trials include insomnia, abnormal dreams, sleep disorders, fatigue and somnolence (all common) and panic reaction, bradyphrenia, thinking abnormal, mood swings, restlessness, malaise, circadian rhythm sleep disorder and anorexia (all uncommon).

Psychiatric adverse events from post-marketing experience in the data sheet include depressed mood, agitation, hallucinations, changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, suicidal ideation and suicide.

The IMMP report concludes that there is a causal relationship for the majority of these events and that psychiatric reactions including 'sleep disturbances' and 'symptoms of depression' are common adverse reactions to varenicline.

The IMMP report notes that an important confounding factor for psychiatric events is smoking cessation which may cause symptoms of psychiatric illness in some patients and that other important potential confounders are a past medical history of psychiatric illness and concomitant medications.

The IMMP report recommends that the data sheet needs strengthening and should include the New Zealand frequency of adverse events.

In December 2009, the MARC was presented with a report following completion of the first year of follow up of the IMMP cohort. Psychiatric events accounted for one third of all events identified in the IMMP study at this time. The MARC noted that the majority of these events were now listed in the Champix data sheet. The MARC agreed that no regulatory action was required at the time and that Medsafe would report back to the MARC as necessary.

In May 2009, a *Prescriber Update* article was published on psychiatric reaction with varenicline following a recommendation from the MARC (3).

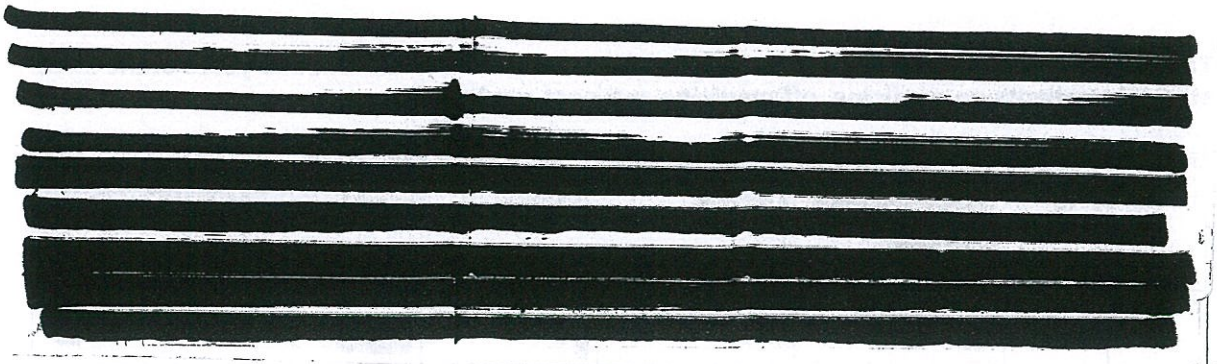
Medsafe comment
The IMMP report concludes that there is a causal relationship for the majority of these events. However, only a couple were assessed by the IMMP as having a certain causal relationship with varenicline.

The data sheet for varenicline currently contains a precaution regarding psychiatric symptoms and psychiatric adverse events from post-marketing experience. From the evidence in the report, Medsafe consider that the data sheet currently contains sufficient information regarding psychiatric events.

It is not normal to add rates from an observation study unless there is a comparator group and a calculated HR/OR.

The sponsor is currently conducting a phase 4, randomized, double-blind, active and placebo-controlled, multi-centre study evaluating the neuropsychiatric safety and efficacy of 12 weeks varenicline tartrate 1mg BID and bupropion hydrochloride 150mg BID for smoking cessation in subjects with and without a history of psychiatric disorders. This safety study is due to be completed 2016/2017.

The sponsor has recently completed a safety study on varenicline use compared with placebo in patients with a current or past diagnosis of major depressive disorder (Annex 9). Subjects in the varenicline group had a higher likelihood of quitting at week 12 [redacted] *and at week 52* [redacted] *Psychiatric scales were included for safety assessment and did not show a difference between the two groups.* [redacted]



In a recent US study on current smoking, adults aged greater than or equal to 18 years who had a mental illness had a smoking rate that was 70% higher than adults with no mental illness (36.1% v 21.4%)(7). The average number of cigarettes smoked in the preceding month was higher among adults with a mental illness (7). In addition, adult smokers with a mental illness were found to be less likely to quit than adults without mental illness. This highlights the need for increased access to prevention and cessation efforts in this population.

Recently, another study in patients who were attending smoking cessation clinics found that those who relapsed six months after treatment had significantly higher anxiety scores than those who remained abstinent (8). The increase in anxiety scores from baseline in patients that relapsed to smoking was largest in patients with a current psychiatric disorder.

3.4.2 Suicide and Suicidal Ideation

Suicide and suicidal ideation adverse events were identified in patients for the first three years of the study (12,839). Deaths were identified from IMMP questionnaires, spontaneous reports and linkage to national mortality data sets.

All cases of completed suicide and fatal overdose were included in the report including those that occurred up to six months after stopping varenicline. Each completed suicide case that was identified was followed up for further information from the patient's doctor. Post-mortem reports and coroner's reports were obtained where possible.

There were five cases of completed suicide and one case of fatal overdose (Table 15). Of the six cases, one occurred whilst the patient was on varenicline treatment, two occurred within a month of stopping and three occurred two to six months following varenicline treatment. Three of the six cases appear to have a history of depression. The IMMP report estimates the risk of completed suicide at 2–5 per 10,000 patients for patients that are on-medicine, off-medicine and post-medicine.

Table 15: Completed suicides and fatal overdoses identified in the first three years of the IMMP study for patients <u>on-medicine</u>, <u>off-medicine</u> and <u>post-medicine</u>

Report Number	Sex, Age	Varenicline treatment	Adverse Events whilst on treatment	Time from last dose to death	Date of death	Comments
D84971	M, [redacted]	[redacted]	? Depression	On medicine	[redacted]	Reported to be on anti-depressants Info lacking about this case [redacted]
H95665	M, [redacted]	[redacted]	Nil reported URTI (off med) Dreams	[redacted] days	[redacted]	Death identified from NZHIS (est [redacted] after end of [redacted]
H97205	M, [redacted]	[redacted]	Nil reported	[redacted] days	[redacted]	No other medicines No history of depression
F93415	F, [redacted]	[redacted]	Insomnia Depression, worse	[redacted] days	[redacted]	Worsening depression did not resolve on cessation of varenicline treatment
H95131	M, [redacted]	[redacted]	Headaches	[redacted] days	[redacted]	Coroners report mentions possible depression
H97929	F, [redacted]	[redacted]	BCC	[redacted] days	[redacted]	[redacted]

In addition, there were:

- two reports of suicide attempts (**R85041** on-medicine and **H96377** off-medicine)
- one report of suicide attempt recurrent (**F90023** off-medicine)
- two reports of intentional overdose (**F83212** and **F93811** both on-medicine)
- one report of intentional overdose recurrent (**H88619** on-medicine).

Of the six cases, five were assessed as having a 'possible' causal relationship with varenicline.

Another four reports of intentional overdose were identified occurring more than one month after stopping varenicline. However, all four cases post-medicine were assessed as 'unlikely' or 'unclassifiable'.

There were nine reports of non-fatal overdose identified of which:

- one occurred in a patient taking varenicline (**H95813**)
- two within a month of stopping treatment (**H89071** and **H93373**)
- six occurred more than one month after stopping varenicline (one of these reports is the same patient who had reported a suicide attempt off-medicine).

A 'possible' causal association was considered in three of non-fatal overdose cases (two off-medicine reports and one post-medicine report). The report of overdose whilst the patient was taking varenicline was assessed as unclassifiable.

There was also one report of intentional self-injury worse in a patient taking varenicline. This patient was reported to have a history of self-harm. This report was assessed as probably associated with varenicline treatment.

Suicidal ideation was identified in 16 reports that occurred while the patient was taking varenicline (Table 16).

In order to further evaluate whether the suicidal ideation experienced by these patients might have been due to smoking cessation itself, cases were examined for further information regarding smoking status. Of the 16 cases of suicidal ideation identified, there were two cases where the patient continued to smoke during varenicline treatment. The IMMP report notes that as both of these patients continued to smoke whilst taking varenicline the suicidal ideation was not likely to be due to smoking cessation.

1. **D87063**: a [redacted] woman with no previous history [redacted] who reported feeling suicidal after [redacted] varenicline treatment.
2. **F92431**: a [redacted] woman with no previous history [redacted] who reported feeling suicidal after [redacted] varenicline treatment

Of the 16 reports of suicidal ideation identified, 14 reports had a positive dechallenge. The IMMP report estimates the frequency of suicidal ideation is patients taking varenicline as 12–17 per 10,000 patients.

Table 16: IMMP reports of suicidal ideation for patients in the first three years of the IMMP study

Report No[1] Age (y) Sex (M/F)	Event	Concurrent events	Dose	Onset[2]	Action/ Outcome	Severity[3]	Causality	Past History	Concomitant meds	Smoking status
F81568 [redacted] F	Suicidal Ideation	Agitation, anxiety, sleep disturbance depression	[redacted]	[redacted]	Withdrawn Not yet recovered	2	Possible	[redacted]	Atenolol	Stopped smoking between [redacted] day of treatment and unknown if remained abstinent
D81761 [redacted] F	Suicidal Ideation	Depression	[redacted]	[redacted]	Withdrawn Improved (over [redacted]	2	Probable	[redacted]	No info	No information
R82695 [redacted] M	Suicidal Ideation	Depression Irritability	[redacted]	[redacted]	Withdrawn Improved	2	Probable	[redacted]	Nil	No information
D83209 (unk) [redacted] F	Suicidal Ideation	Depression	[redacted]	[redacted]	Withdrawn Improved	2	Probable	[redacted]	Nil	No information
R83495 [redacted] F	Suicidal Ideation	–	[redacted]	[redacted]	Withdrawn Improved	1	Probable	[redacted]	Nil	No information
D&F84975 [redacted] F	Suicidal Ideation [redacted] Course[4]	Depression, worse ?overdose	[redacted]	[redacted]	Withdrawn Improved	1	Possible	[redacted]	No info	Unknown
D87063 (unk) [redacted] F	Suicidal Ideation	Constipation	[redacted]	[redacted]	Withdrawn Improved	2	Probable	[redacted]	Nil	Did not stop
F87138 [redacted] F	Suicidal Ideation	Depression Constipation	[redacted]	[redacted]	Withdrawn Unknown	1	Possible	[redacted]	Nil	Stopped smoking between [redacted] day of treatment but restarted
F87139 [redacted] M	Suicidal Ideation	Paroniria Depression Aggression	[redacted]	[redacted]	Withdrawn Improved	2	Probable	[redacted]	Nil	Stopped smoking after [redacted] day of treatment and remained abstinent with hypnosis
R&F88331 [redacted] F	Suicidal Ideation	Depression, worse	[redacted]	[redacted]	Withdrawn Improved	1	Probable	[redacted]	Citalopram oestrogens conjugated	Stopped smoking between [redacted] day of treatment but restarted
R89495 [redacted] F	Suicidal Ideation	Depression, worse	[redacted]	[redacted]	Withdrawn Improved (after [redacted])	2	Probable	[redacted]	Metformin oestrogens conjugated, clonidine, omeprazole, temazepam, simvastatin	Stopped smoking [redacted] month before onset of suicidal ideation
R&F91748 [redacted] F	Suicidal Ideation [redacted] Course[4]	Irritability	[redacted]	[redacted]	Withdrawn Improved (within [redacted])	1	Probable	[redacted]	Oestrogens conjugated	Unknown
F92431 [redacted] F	Suicidal Ideation	–	[redacted]	[redacted]	Withdrawn Improved	2	Probable	[redacted]	Nil	Did not stop
F93903 [redacted] F	Suicidal Ideation	–	[redacted]	[redacted]	Withdrawn Improved	2	Probable	[redacted]	Nil	Stopped smoking between [redacted] day of treatment, but restarted
R97360 [redacted] F	Suicidal Ideation [redacted] Course[4]	Depression, worse	[redacted]	[redacted]	Withdrawn Improved (afte [redacted]	2	Probable	[redacted]	Naproxen, loratadine, symbicort	No information
D94711 [redacted] M	Suicidal Ideation -Self harm thoughts	Paranoia Emotional lability	[redacted]	[redacted]	Withdrawn Improved	2	Probable	[redacted]	Nil	Stopped smoking [redacted] week before onset of self harm thoughts

[1] Prefix denotes source of report F=questionnaire, D=drug company and R=spontaneous report
[2] Unit for time to onset h=hours, d=days, w=weeks and m=months
[3] Severity 1=severe and 2=not severe
[4] Course = course of varenicline

The data sheet for varenicline currently contains the following precaution about neuropsychiatric symptoms including suicidal ideation and suicidal behaviour (1).

> ***Precautions>Psychiatric Symptoms***
> *Serious neuropsychiatric symptoms have occurred in patients being treated with CHAMPIX. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking; however, some of these symptoms have occurred in patients who continued to smoke. Although a causal association between CHAMPIX and these symptoms has not been established, in some reports the association cannot be excluded. Patients being treated with CHAMPIX and their families, should be alerted to the need to monitor for neuropsychiatric symptoms including changes in behaviour or thinking, anxiety, psychosis, mood swings, agitation, aggression, depressed mood, suicidal ideation and suicidal behaviour. Doctors should discuss the efficacy and safety profile of CHAMPIX with patients attempting to quit smoking with CHAMPIX and advise them of the possible emergence of neuropsychiatric symptoms. These symptoms, as well as worsening of pre-existing psychiatric illness, have been reported in patients attempting to quit smoking while taking CHAMPIX in the post-marketing experience. Patients and their families, should be advised that the patient should stop taking CHAMPIX and contact a health care professional immediately if changes in behaviour or thinking, agitation or depressed mood, that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behaviour In many post-marketing cases, resolution of symptoms after discontinuation of CHAMPIX was reported, although in some cases the symptoms persisted; therefore, ongoing follow up should be provided until symptoms resolve. Patients and their families should be encouraged to report any history of psychiatric illness prior to initiating treatment. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHAMPIX and the safety and efficacy of CHAMPIX in such patients has not been established.*

The data sheet also mentions that there has been post-marketing reports of neuropsychiatric symptoms such as suicidal ideation and suicide in patients attempting to quit smoking while taking Champix.

The IMMP report concludes that suicidal ideation is causally associated with varenicline treatment and recommends that Medsafe consider whether the data sheet needs to be strengthened but have not provided details of how or proposed wording.

Medsafe comment
The only case of completed suicide reported whilst the patient was taking medicine had limited information [redacted] Two of the remaining five cases of completed suicide that occurred off-medicine or post-medicines appear to have a history of depression and one case had basal cell carcinoma. Concomitant medications, medical history and smoking status are not known in all cases. The report does not provide sufficient evidence to assess causality for suicide and does not compare the incidence against the background incidence. No evidence is presented to show that varenicline had induced a series of effects resulting in suicide in patients no longer taking varenicline.

To determine if the reports of attempted suicide or intentional overdose were causally related to varenicline treatment more information is necessary including concomitant medication, smoking status and psychiatric history.

There were 16 reports of suicidal ideation were identified in patients taking varenicline. Of the 16 reports, seven patients had a history of depression. Smoking status was unknown in seven reports.

The New Zealand data sheet for varenicline contains a precaution regarding psychiatric symptoms that includes information about the need to monitor patients for neuropsychiatric symptoms and that the patient should stop taking varenicline and contact a healthcare professional immediately if changes in behaviour or thinking, agitation or depressed mood, that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behaviour.

The IMMP report concludes that suicidal ideation is causally associated with varenicline but has not acknowledged the limitations of the data including other medicines, relevance of past medical history, social factors and potential triggers.

Suicide-related events are routinely monitored by the sponsor in the PSUR. In the latest PSUR, no new safety concerns were identified as a result of the review of the cases.

The company is currently conducting a safety study in patients with and without a history of psychiatric disorders. This may provide further information.

Medsafe considers, given the evidence provided in the IMMP report, the current data sheet contains sufficient warning about suicide and suicide ideation.

3.4.3 Memory Impairment

There were six reports of memory impairment identified in the first three years of the IMMP study (Table 17). Further analysis identified seven more reports in the total four year cohort (Table 17). The results of this IMMP review were published online as a letter to the editors in the *European Journal of Clinical Pharmacology* in December 2012 (9) (Annex 10).

Of the 13 cases, four were considered severe and 11 patients were less than 60-years-old at the time of the report. The four severe cases included one patient describing 'periods of total memory loss', one patient forgetting to collect her children on three occasions and one patient reporting to her doctor that memory loss affected her ability to work.

In nine of the 13 cases, varenicline treatment was withdrawn and eight of these patients reported an improvement. The IMMP assessed the relationship of memory impairment with varenicline as probable in nine cases, possible in three cases and unclassifiable in one case.

The IMMP report notes that possible confounders such as smoking status and medical history were considered in the causality assessment.

The IMMP report concludes that 12 or the 13 reports suggest a causal relationship between varenicline and memory impairment.

Table 17: IMMP reports of memory impairment identified during the four year IMMP study

Case No	Age/ Sex	Dose[1] (mg)	Onset[2] (Dur tx)[3]	Severe	Action[4]/ Outcome	IMMP Causality[5]	Concurrent Events	Concomitant Medicines
1	F	[redacted]	[redacted]	Yes	Withdrawn/ Improved	2	Depression	Zopiclone, nortriptyline (for pre-existing insomnia)
2	M	[redacted]	[redacted]	Yes	Withdrawn/ Improved	2	Thinking abnormal	
3	F	[redacted]	[redacted]	Yes	Withdrawn/ Improved	2	TIA-like events, dizziness, blurred vision, hyperthyroidism	
4	F	[redacted]	[redacted]	Yes	Withdrawn/ No improvement	3	Anxiety, menopausal symptoms	
5	F	[redacted]	[redacted]	No	Withdrawn/ Improved	2	Poor concentration, depression	Conjugated estrogens
6	M	[redacted]	[redacted]	No	Med continued Improved	3	Irritability, worse	
7	M	[redacted]	[redacted]	No	Withdrawn/ Improved	2	Anxiety	
8	M	[redacted]	[redacted]	No	Withdrawn/ Improved	2	Dry Mouth	
9	F	[redacted]	[redacted]	No	Withdrawn/ Improved	2	Nightmares, depression, poor concentration, weight increased, constipation	Amitriptyline, omeprazole bendrofluazide (all started prior to varenicline)
10	M	[redacted]	[redacted]	No	Med continued Improved	3	Nil reported	
11	F	[redacted]	[redacted]	No	Withdrawn/ Improved	2	Nausea, bloating	
12	F	[redacted]	[redacted]	No	Dose reduced Improved	2	Sweating, sleep disturbance, malaise	
13	M	[redacted]	[redacted]	No	Unknown/ Unknown	6		

[1] Daily dose of varenicline at time of adverse event
[2] Time to onset of memory impairment after starting varenicline
[3] Total duration of varenicline treatment
[4] Action taken regarding varenicline treatment
[5] Relationship of memory impairment with varenicline according to causality assessment performed at the IMMP. Relationship 2 = 'probable', 3 = 'possible', 6 = 'unclassifiable'

The Canadian Institute for Safe Medication Practices (ISMP) has reported nine cases of memory impairment identified in the FDA data sets for varenicline and suggest this may be linked to vasodilation or vasoconstriction. However, no information about the cases is provided (10).

Memory impairment is not listed in the New Zealand data sheet for varenicline. The varenicline data sheet states that difficulty concentration has been associated with smoking cessation with or without treatment. Thinking abnormal and bradyphrenia are also listed as a adverse events in the New Zealand data sheet. The US product label states that amnesia and mental impairment was reported during clinical trials. The UK summary of product characteristics lists difficulty concentrating.

The report concludes that further research is needed to investigate whether the memory impairment is part of a spectrum of psychiatric events or whether it is related to cardiovascular effects. The report recommends that Medsafe ask the sponsor to include memory impairment in the varenicline data sheet.

Medsafe comment
Of the 13 cases, one patient had insufficient information to assess causality, two patients were likely going through menopause, one patient's memory improved while continuing with treatment and two patients were also being treated with a TCA.

It would have been informative to get a description of the types of memory impairment for all 13 cases and to find out the patient's smoking status. No information was provided on memory prior to varenicline treatment, concurrent illness or medical history. It is also

important to determine the background incidence of memory impairment in patients stopping smoking.

Risk factors such as interacting medicines and other drugs of abuse should be reviewed by IMMP.

In addition, difficulty concentrating is an expected event following smoking cessation and is listed in the data sheet as associated with smoking cessation with and with treatment.

In the recent PSUR for Champix, the sponsor reviewed the safety topic of memory impairment/amnesia and noted no new safety concerns.

3.4.4 Cardiovascular Adverse Events

The data presented in the final IMMP report includes all adverse events in the circulatory group identified in patients in the first three years of the study. The profile of adverse events in this report is similar to that presented to the MARC in September 2011.

Following the review of the issue of varenicline and cardiovascular events by the MARC in September 2011, the MARC considered that although cardiovascular related safety concerns have been raised in association with varenicline, a causal relationship has yet to be demonstrated. The MARC recommended that the Champix data sheet be updated to include information about reports of cardiovascular related adverse events associated with the use of varenicline. The Champix data sheet was updated in line with wording contained in the Australian Product information, as recommended by the MARC.

The varenicline data sheet was updated in May 2012 to include information about cardiovascular events in the precautions section (1). The data sheet has also recently been updated to include information about a study in subjects with cardiovascular disease in the clinical trials section.

Precautions>Cardiovascular Events
In a single smoking cessation trial of patients with stable cardiovascular disease, while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with varenicline. No causal relationship between these events and varenicline has been established. Smoking is an independent and major risk factor for cardiovascular disease (See CLINICAL TRIALS – Study in Subjects with Cardiovascular Disease).

Adverse Effects>Post-marketing Experience
There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischaemic and haemorrhagic events in patients taking CHAMPIX. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.

Clinical Trials>Study in Subjects with Cardiovascular Disease
Varenicline was evaluated in a randomised, double-blind, placebo-controlled study of 703 subjects with stable, documented cardiovascular disease (other than or in addition to hypertension) that had been diagnosed for more than 2 months. Subjects aged 35 to 75 years were randomised to varenicline 1 mg twice a day or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47.3 %) compared to subjects treated with placebo

(14.3%) (odds ratio 6.05; 95% CI 4.13, 8.86; p<0.0001) and from week 9 through 52 (19.8%) compared to subjects treated with placebo (7.4%) (odds ratio 3.19; 95% CI 1.97, 5.18; p<0.0001). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment-emergent and non-treatment-emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency ≥ 1% in either treatment group: nonfatal myocardial infarction (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs 1.1%). During non-treatment follow up to 52 weeks, adjudicated events with a frequency ≥1% included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52 week study. The key results are summarized in the following table:

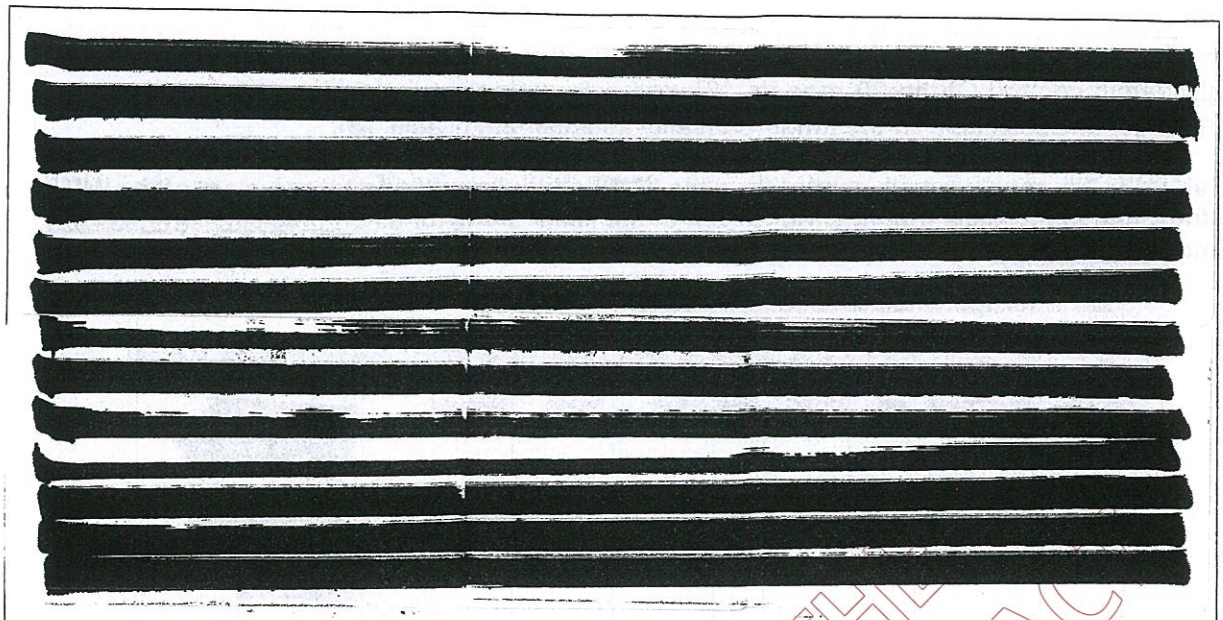
Table: Rates of carbon monoxide-confirmed abstinence for study in subjects with cardiovascular disease

	Varenicline n=353	***Placebo n=350***	***Odds ratio (95 % CI) p value***
Continuous abstinence wk 9–12	*47.3 %*	*14.3 %*	*6.05 (4.13, 8.86) p<0.0001*
Continuous abstinence wk 9-52	*19.8 %*	*7.4 %*	*3.19 (1.97, 5.18) p<0.0001*

In addition, atrial fibrillation and palpitations are listed as uncommon adverse events observed during clinical trials.

Recently, another meta-analysis of cardiovascular events identified in varenicline clinical trials has been published (11). This review included 22 clinical trials and concluded there was no increased risk of cardiovascular events with varenicline. This article was included in the MARC dossier of the June 2012 meeting.

Medsafe comment
Following a request from the FDA, the company performed a meta-analysis of varenicline randomized, blinded, controlled clinical trials with treatment duration of 12 weeks or longer to evaluate cardiovascular safety of varenicline. The company has provided Medsafe with a copy of the final report (Annex 11). The primary endpoint was adjudicated major adverse cardiovascular events (MACE) that occurred during treatment. [redacted] *The primary endpoint results of this meta-analysis are shown in Figure 2.*



Of note, not all the studies were directed to look at cardiovascular events and the majority of the events were from one study Rigotti et al (12). The Rigotti et al. study was reviewed by the MARC in September 2011. The MARC noted that the Rigotti et al. study was not designed or sufficiently powered to be able to detect a small but significant difference in event rates.

The company concluded that the results of this meta-analysis showed no statistically significant difference for the primary and secondary endpoints. The company intends to mention the nature of the findings from this cardiovascular meta-analysis in the varenicline New Zealand data sheet.

The FDA has requested a further study (called 'CAT') of approximately 8000 patients (comparing varenicline, bupropion and nicotine replacement therapy) with the study designed to have major cardiovascular events as a primary outcome. The results of this study are not due to be published until 2017.

Medsafe comment
The IMMP report contains no additional information than that presented to the MARC in September 2011.

Medsafe considers that no further action be taken at present and that the 'CAT' study be reviewed when published.

3.4.5 Glycaemic Control

In April 2011, Health Canada reported a possible link between varenicline and hyperglycaemia in known Type 1 and Type 2 diabetics and a case series of 18 reports was published in the Canadian Adverse Reactions Newsletter (13).

Following this report, IMMP reviewed all reports of new-onset hyperglycaemia, impaired glucose tolerance, diabetes mellitus, non-insulin-dependent diabetes mellitus and worsening diabetes mellitus in the cohort. The cohort reviewed in this instance is the first three years of the IMMP study and some cases from the final year. All events occurring whilst taking varenicline and within one month of the last dose and events occurring between one and six months after the last dose of varenicline were included.

In the varenicline events data set at May 2012, there were 29 reports suggesting altered glycaemic control. Of the 29 reports, 10 were categorised as 'possible', 16 as 'unlikely' and three as 'unclassifiable' in the IMMP causality assessment (Table 18).

Table 18: Altered glycaemic control from the IMMP study from the first three years of the IMMP study and some cases from the fourth year of the IMMP study for all <u>on-medicine</u>, <u>off-medicine</u> and <u>post-medicine</u> reports

Table 1: IMMP reports of Varenicline and Altered Glycaemic Control

Report No Age/Sex	Events	Onset	Time from last dose	Dose mg	Dechallenge	Causality Assessment	Concomitant Meds	Additional Information
F83355 M	Hyperglycaemia Polyuria Polydipsia Blurred vision	[redacted]	On med	[redacted]	Negative	Possible	Nil reported	[redacted]
F91151 M	Hyperglycaemia Reflux Inguinal hernia	[redacted]	On med	[redacted]	Positive	Possible	Aspirin simvastatin omeprazole	[redacted]
F09857 M	Hyperglycaemia Pompholyx	[redacted]	On med	[redacted]	Negative	Possible	Accupril simvastatin	[redacted]
F09707 M	Hyperglycaemia	[redacted]	[redacted]d	[redacted]	Off med	Possible	Cilazapril, simvastatin, omeprazole	[redacted]
F84127 M	Hyperglycaemia (post-medicine)	[redacted]	[redacted]m	[redacted]	Off med	Unlikely	Fluoxetine, omeprazole, simvastatin, felodipine, Inhibace Plus	[redacted]
F82142 M	Impaired GTT	[redacted]	On med	[redacted]	Negative	Unlikely	No	[redacted]
F91125 M	Impaired GTT	[redacted]	On med	[redacted]	Med cont	Possible	Nil reported	[redacted]
F97685 M	Impaired GTT (post-medicine)	[redacted]	[redacted]l	[redacted]	Off med	Unlikely	Nil	[redacted]
F81993 F	NIDDM	[redacted]	[redacted]d	[redacted]	Off med	Possible	Symbicort, aspirin, felodipine, paroxetine	[redacted]
F91762 F	NIDDM Weight increase Sleep disturbed	[redacted]	[redacted]d	[redacted]	Off med	Possible	Simvastatin	[redacted]
F92164 F	NIDDM LRTI Hysterectomy	[redacted]	[redacted]d	[redacted]	Off med	Unlikely	Nil reported	[redacted]
F96636 F	NIDDM Hypertension	[redacted]	[redacted]d	[redacted]	Off med	Unlikely	Verapamil, bendrofluazide	[redacted]
F85924 F	NIDDM (post-medicine)	[redacted]	[redacted]d	[redacted]	Off med	Unlikely	Metoprolol,aspirin, simvastatin, fluoxetine	[redacted]

Report No Age/Sex	Events	Onset	Time from last dose	Dose mg	Dechallenge	Causality Assessment	Concomitant Meds	Additional Information
H96925 M	NIDDM (post-medicine)		d		Off med	Unlikely	No info	
F91140 M	NIDDM (post-medicine)		d		Off med	Unlikely	Aspirin	
F98199 F	DM (post-medicine)		d		Off med	Unlikely	Nil reported	
H90013 M	DM (post-medicine)		d		Off med	Unlikely	Cilazapril, aspirin, felodipine, loratadine bendrofluazide	
H92743 F	DM worse		On med		No info	Unclassifiable	No info	
H92869 M	DM worse		On med		No info	Unclassifiable	No info	
H94133 M	DM worse		On med		Negative	Unlikely	Cilazapril, aspirin, simvastatin, insulin aspart, isophane insulin, gabapentin, dothiepin, citalopram	
F91398 F	DM worse		On med		Negative	Unlikely	Protophane insulin, novorapid insulin, accupril, venlafaxine, thyroxine, metformin	
H93453 F	DM worse		d		Off med	Unlikely	No info	
F91391 M	DM worse Increased appetite		On med		No info	Possible	Inhibace Plus, simvastatin, aspirin, insulin	
F96262 M	DM worse Hyperlipidaemia worse		d		Off med	Possible	Aspirin, enalapril, metformin, metoprolol, simvastatin	
D98235 M	DM worse Abscess, Periodontitis		On med		No info	Unclassifiable	Subcutaneous insulin glargine, lispro	
D97511 F-No ID	DM worse		On med		Positive	Possible	Insulin	
F87832 F	DM worse (post-medicine)		d		Off med	Unlikely	Cilazapril,simvastatin, omeprazole, metoprolol, aspirin, citalopram	
F99448 F	DM worse(post-medicine)		d		Off med	Unlikely	Insulin	
H96048 M	Diabetic Ketoacidosis (post-medicine)		d		Off med	Unlikely	Insulin	

The 29 reports identified in the IMMP study include:

- 5 reports of new-onset hyperglycaemia (4 'possible')
- 3 reports of new-onset impaired glucose tolerance (1 'possible')
- 9 reports of new-onset diabetes (2 'possible')
- 11 reports of diabetes worse (3 'possible')
- 1 report of diabetic ketoacidosis (0 'possible')

The IMMP report notes that as most patients were not screened for diabetes at the time of commencing varenicline treatment, pre-existing abnormal glycaemic control may have remained undiagnosed, leading to these events being misclassified as new ones.

Increased appetite and weight gain associated with smoking cessation may alter glycaemic control in diabetics and latent diabetics and therefore are possible confounding factors in this review. Of the 29 cases in this series, two patients were also reported to have experienced weight gain at the time of developing altered glycaemic control and it is possible that other patients experienced weight gain which was not reported, but which may have contributed to their altered glycaemic control.

The New Zealand data sheet contains the following precaution about the effects of smoking cessation (1).

> ***Precautions>Effects of Smoking Cessation***
> *Physiological changes resulting from smoking cessation, with or without treatment with CHAMPIX, may alter pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.*

The New Zealand varenicline data sheet also currently lists glycosuria and polyuria as uncommon adverse events identified in clinical trials.

The IMMP report considers that the study has not obtained sufficient evidence to confirm or refute a causal relationship between varenicline and loss of glycaemic control in diabetic patients. Causality assessment determined the relationship with varenicline was 'possible' for seven of the 10 new-onset cases.

For both the cases of altered glycaemic control in known diabetics and the new-onset cases, assessment was often restricted by insufficient information and confounded by possible dietary factors, changes in weight, lack of compliance with hypoglycaemic agents, and also infection, illness or other factors.

The report concludes that the IMMP study has identified a possible signal of new-onset altered glycaemic control in patients taking varenicline and should be researched further. The author suggests a randomized control trial of diabetic patients (who were not included previously in premarketing trials) taking varenicline should be undertaken in order to investigate the issue of new-onset altered glycaemic control.

Medsafe comment
It is unclear if all the final year reports were examined for cases of glycaemic control or just the cases that had successfully been followed up as the final year dataset has yet to be data locked. This is inconsistent with the other adverse events examined.

Many of the patients had stopped taking varenicline weeks to months before the adverse event. Of the reports of altered glycaemic control, none were assessed as having a 'probable' relationship with varenicline and only 10 of the 29 reports were assessed as having a 'possible' relationship with varenicline. The majority of the cases had confounding factors or insufficient information. In addition, the patient's current smoking status was not presented.

Diabetes mellitus/hyperglycaemia has been reviewed by the sponsor in PSURs 3 through to 9. In most cases in the recent PSUR where sufficient information was reported, other risk factors for glucose abnormalities were present which may have played a role consistent with the findings from the previous PSURs. The sponsor will continue to review this topic in the next PSUR and discuss if a new safety concern is identified.

Increased appetite is associated with smoking cessation and nicotine withdrawal, and this change in dietary behaviour can affect glycaemic control. The New Zealand data sheet currently contains information about the physiological changes resulting from smoking cessation including a precaution that dose adjustments of insulin may be required during smoking cessation.

Medsafe considers that the New Zealand data sheet contains sufficient information regarding glycaemia control and no changes to the current New Zealand are warranted at this time.

3.4.6 Adverse Events in the Eye

The IMMP study undertook a review of all reports coded and entered into the eye group during the first three years of the study. All events of visual disturbance coded as blurred vision, and abnormal vision were identified and tabulated. Other event reports that might have included symptoms of abnormal vision (eg, eye pain and conjunctivitis) were also reviewed to check the initial coding and ensure all reports of visual disturbance had been correctly coded and included in this review.

There were 39 events identified in the eye group, 37 that occurred whilst taking varenicline and two that occurred within one month of stopping (Table 19).

In the three year period of the report, there were six reports of blurred vision and two reports of abnormal vision (Table 20). The IMMP assessed five reports as having a causal association (three 'probable' and two 'possible'). From the reports that IMMP assessed to be causal, four were associated with migraine or headache.

Table 19: Reports of varenicline and eye events in the first three years of the IMMP study (From Annex 6)

		Medsafe cohort n=12,839			
Clinical sub-group	Event	Number on med events	Rate per 1000 pts	Number off-med events	Rate per 1000 pts
Vision disorders	Blurred vision	6	0.47	0	0.00
	Vision abnormal	2	0.16	0	0.00
	Sub-group total	8	0.62	0	0.00
Pain/inflammation	Eye pain	2	0.16	0	0.00
	Eyes irritable	3	0.23	0	0.00
	Eyes watering	1	0.08	0	0.00
	Red eyes	1	0.08	0	0.00
	Ophthalmitis	1	0.08	0	0.00
	Conjunctivitis	5	0.39	0	0.00
	Conjunctivitis allergic	1	0.08	0	0.00
	Uveitis anterior	1	0.08	0	0.00
	Episcleritis	1	0.08	0	0.00
	Sub-group total	16	1.25	0	0.00
Eyelid disorders	Blepharitis	2	0.16	0	0.00
	Stye	1	0.08	0	0.00
	Eyelid disorder NOS	0	0.00	1	0.08
	Sub-group total	3	0.23	1	0.08
Other	Optic neuropathy	1	0.08	0	0.00
	Optic disc naevus	1	0.08	0	0.00
	Cataract	3	0.23	0	0.00
	Anisocoria	1	0.08	0	0.00
	Sub-conjunctival haemorrhage	0	0.00	1	0.08
	Pterygium	1	0.08	0	0.00
	Photophobia	1	0.08	0	0.00
	Corneal ulcer	2	0.16	0	0.00
	Sub-group total	10	0.78	1	0.08
Total		37	2.88	2	0.16

Table 20: IMMP reports of blurred vision and abnormal vision in the first three years of the IMMP study

Report No[1]	Events	Age / Sex	Dose (mg)	Onset	Severe	Action/ Outcome[2]	Causality Assessment	Concomitant Meds	Concurrent Events
R77584	Blurred vision	M	[redacted]	[redacted]	No	Withdrawn Improved	Probable	Salbutamol, bendrofluazide, symbicort	Diarrhoea,heartburn, abdominal pain,dizziness
F82709	Blurred vision	M	[redacted]	[redacted]	No	Med cont No change at end of course	Unlikely	Omeprazole	Thought to be migrainous aura associated with photophobia, seeing spots without headache
R83355	Blurred vision	M	[redacted]	[redacted]	No	Withdrawn Did not improve	Possible		Hyperglycaemia (confirmed diagnosis of diabetes mellitus), polyuria, polydipsia
R84825	Blurred vision	F	[redacted]	[redacted]	No	Withdrawn Improved	Probable	Pantoprazole	Migraine more frequent,nausea, dizziness, aggression
F86996	Blurred vision	M	[redacted]	[redacted]	No	Withdrawn No info	Possible	None reported	Headache
F91325	Blurred vision	M	[redacted]	[redacted]	No	Med cont No info	Unlikely (old injury)	Sodium cromoglycate eye drops	
P83123	Vision abnormal	M	[redacted]	[redacted]	No	Med Cont No info	Unclassifiable		Migraine
F85525	Vision abnormal	M	[redacted]	[redacted]	No	Withdrawn Improved	Probable	Ranitidine, venlafaxine,clonazepam, acetylsalicylic acid , symbicort	Nausea, abdominal discomfort, dry mouth

The New Zealand varenicline data sheet lists the following as uncommon events in the eye disorders in the adverse events from clinical trials (1):

- scotoma
- scleral discolouration
- eye pain
- mydriasis
- photophobia
- myopia
- lacrimation increased

The New Zealand varenicline data sheet also lists headache as a common adverse event that occurred during clinical trials (1).

The report concludes that eight reports of impaired vision were identified while the patient was on varenicline. IMMP assessed five of the eight reports as having a causal relationship with varenicline.

IMMP recommends that this issue warrants further investigation and recommend that Medsafe request the sponsor to include blurred vision and visual disturbance as adverse reactions in the New Zealand varenicline data sheet.

Medsafe comment
The IMMP study concludes that five of the reports had a causal relationship with varenicline; three were assessed as having a 'probable' relationship with varenicline. However, many of these five cases are confounded by concurrent illness, medical history or concomitant medications.

In the recent PSUR for Champix, the sponsor reviewed the safety topic of vision disorders and noted no new safety concerns.

The New Zealand data sheet currently contains scotoma, mydriasis, myopia and photophobia as uncommon adverse events and headache as a common adverse event.

Medsafe considers that the New Zealand data sheet contains adequate information regarding adverse events in the eye and no changes are warranted at this time.

3.4.7 Haematological Events

In the first three years of the IMMP study, there were 19 adverse events in the haematological group that occurred whilst the patient was taking varenicline or within one month of stopping (Table 21). Of the 19 adverse events, 10 occurred whilst the patient was taking the medicine.

There were three bleeding events (**P87035**, **R77936** and **H85448**) and two epistaxis events (**F91385** and **F92131**) the patient was taking varenicline. Of the three bleeding reports, two reports were specifically bleeding of the gums (**P87035** and **R77936**). Report **R77936** is confounded by the patient taking warfarin and report **H85448** was assessed as unlikely to have a causal relationship with varenicline.

Table 21: Haematological events in the first three years of the study

		Medsafe cohort n=12,839			
Clinical sub-group	Event	Number on-med events	Rate per 1000 pts	Number off-med events	Rate per 1000 pts
Anaemia	Anaemia Fe deficient	0	0.00	1	0.08
	Fe deficiency	1	0.08	0	0.00
	Ferritin decreased	1	0.08	0	0.00
	Anaemia NOS	0	0.00	3	0.23
	Sub-group total	2	0.16	4	0.31
Bleeding disorders	Bleeding	3	0.23	0	0.00
	Epistaxis	2	0.16	1	0.08
	Haematoma	1	0.08	1	0.08
	Haemoptysis	0	0.00	1	0.08
	Thrombocytopenia	1	0.08	0	0.00
	Sub-group total	7	0.55	3	0.23
Other	Lymphadenopathy	1	0.08	1	0.08
	Splenic rupture	0	0.00	1	0.08
	Sub-group total	1	0.08	2	0.16
Total		10	0.78	9	0.70

No other information about the events was included in the IMMP report apart from a brief summary of the article published by IMMP in collaboration with Lareb 'Epistaxis and other

haemorrhagic events associated with the smoking cessation medicine varenicline: a case series from two national pharmacovigilance centres' (14).

This paper states 16 haemorrhagic events were identified from New Zealand data, of which nine were assessed as having a causal relationship with varenicline (14).

The New Zealand data sheet contains the following precaution about the effects of smoking cessation (1).

> ***Precautions>Effects of smoking cessation***
> *Physiological changes resulting from smoking cessation, with or without treatment with CHAMPIX, may alter pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.*

The data sheet also includes the following information about warfarin (1).

> ***Interactions with other medicines>Warfarin***
> *Varenicline tartrate (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R,S)-warfarin. Prothrombin time (INR) was not affected by varenicline tartrate. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see PRECAUTIONS).*

The New Zealand data sheet for varenicline lists haematemesis, haematochesia and platelet count decreased as uncommon adverse events that occurred during clinical trials. The data sheet also states that there has been post-marketing reports of haemorrhagic events in patients taking Champix.

> ***Adverse effects>Post-marketing experience***
> *There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischaemic and haemorrhagic events in patients taking CHAMPIX. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.*

The IMMP report discusses several possible mechanisms leading to an increased likelihood of bleeding. The IMMP note that thrombocytopenia is listed as an adverse event in the varenicline data sheet and that low platelets counts are associated with an increased bleeding tendency. The IMMP report also proposes that varenicline could affect serotonin levels by affecting serotonin re-uptake through binding of the 5-HT receptor and transporter system.

The IMMP report mentions that in addition to the confounding issue of a history of smoking in all patients, there may also be the potential confounding effect of smoking cessation itself on the haematological system which may increase the likelihood of bleeding. However, the evidence for smoking cessation resulting in clinically significant bleeding is inconclusive.

The IMMP report concludes that the IMMP study has identified a series of haemorrhagic events associated with varenicline. The majority of reports of nose and gum bleeding were assessed as having a causal relationship with varenicline because of a temporal association and evidence of resolution of the event after varenicline was withdrawn.

The IMMP report includes that it may now be appropriate for Medsafe to request that the sponsor includes a statement regarding post-marketing reports of epistaxis and gingival bleeding.

Medsafe comment
In the first three years of the IMMP study, there were three reports of bleeding and two reports of epistaxis. Of these five reports, one is confounded by concomitant medication and one assessed by IMMP as unlikely causally associated with varenicline.

The IMMP report does not give any addition information about the New Zealand reports of haematological events in the haematological events section other than that in Table 21. No information on the assessment of the cases is included aside from that in the Annexes. Currently no information is known regarding concomitant medication, medical history or smoking status.

The sponsor of varenicline completed a safety review of epistaxis and other haemorrhagic events in the recent PSUR following the publication of the case series by Harrison-Woolrych et al (14). This included a cumulative review of post-marketing reports of haemorrhage as well as reviews of clinical trial data and the published literature. The company considered based on this review, no important new safety information was identified, and no changes to the CCDS are warranted at this time. Cases reporting epistaxis and other haemorrhage events will be reviewed by the company in the next PSUR.

In addition, the company investigated the potential mechanism for increased bleeding proposed by the Harrison-Woolrych case series. The IMMP report proposed that varenicline could affect serotonin re-uptake since platelets are large reservoirs of serotonin in circulation and that decreased levels of platelet serotonin could lead to impairment of platelet aggregation thereby increasing the risk of bleeding and bruising. The company identified several lines of evidence that varenicline would not have an effect on serotonin or serotonergic pathways. In vitro binding affinity studies demonstrate that varenicline has very low binding affinity for serotonin (5-HT) receptors and the 5-HT transporter (Ki > 1000nM, although it has modest affinity for the 5-HT3 receptor whose Ki = 350nM). Steady state free human plasma levels of varenicline following 1mg BID dosing are 20–40nM. Therefore, varenicline at therapeutic levels (20-40nM) following 1mg BID dosing of varenicline would not be able to decrease serotonin stores by blocking serotonin reuptake, nor would it be able to block serotonin receptors some of which mediate platelet aggregation.

The IMMP report also notes that smoking might have a suppressive effect on bleeding and smoking cessation could lead to an increase in bleeding.

The New Zealand data sheet currently contains a warning that dose adjustments of warfarin may be required as smoking induces CYP1A2 and mentions that there has been post-marketing reports of haemorrhagic events in patients taking Champix. Haematemesis, haematochesia and platelet count decreased are listed as uncommon adverse events following clinical trials.

Medsafe considers that based on this report, no changes are warranted to the New Zealand data sheet at this time.

3.4.8 Adverse Events in the Skin

The IMMP reviewed all reports in the first three years of the study that included events coded in the skin group. All events were reviewed to identify cutaneous reactions that may be serious, which was defined as resulting in hospitalisation, life threatening or resulting in death. To assist in identifying serious skin reactions, events within the skin group that had

been coded as 'severe' were identified — although it should be noted that severity describes the intensity of a specific event, rather than the seriousness of that event.

In the first three years of the study, there were 89 events in the skin group that occurred whilst on the medicine or within one month from stopping (Table 22). Of the 89 events, 73 occurred whilst the patient was taking varenicline. The most common adverse events in the IMMP skin group whilst the patient was taking varenicline were rash, pruritus and urticaria.

Table 22: Adverse events in the IMMP skin group in the first three years of the IMMP study

		Medsafe cohort n=12,839			
Clinical sub-group	Event	Number on-med events	Rate per 1000 pts	Number off-med events	Rate per 1000 pts
Urticaria/Angioedema	Angioedema	1	0.08	0	0.00
	Oedema periorbital	3	0.23	0	0.00
	Urticaria	6	0.47	1	0.08
	Urticaria worse	1	0.08	0	0.00
	Sub-group total	11	0.86	1	0.08
Pruritus	Pruritus	7	0.55	1	0.08
	Pruritus ani	1	0.08	1	0.08
	Sub-group total	8	0.62	2	0.16
Eczemas/Rash	Eczema	2	0.16	0	0.00
	Eczema worse	1	0.08	0	0.00
	Rash	1	0.08	0	0.00
	Sub-group total	4	0.31	0	0.00
Dermatitis/Rash	Dermatitis	2	0.16	0	0.00
	Rash	12	0.93	4	0.31
	Rash macular	1	0.08	0	0.00
	Rash desquamating	1	0.08	0	0.00
	Rash itchy	2	0.16	2	0.16
	Skin disorder	0	0.00	1	0.08
	Sub-group total	18	1.40	7	0.55
Vesicular	Rash	1	0.08	0	0.00
	Sub-group total	1	0.08	0	0.00
Solar	Solar keratosis	1	0.08	1	0.08
	Sub-group total	1	0.08	1	0.08
Scaling	Psoriasis	2	0.16	0	0.00
	Psoriasis worse	1	0.08	0	0.00
	Pityriasis rosea	1	0.08	0	0.00
	Keratosis	0	0.00	1	0.08
	Keratosis seborrhoeic	4	0.31	0	0.00
	Sub-group total	8	0.62	1	0.08
	Acne	3	0.23	0	0.00
	Follicular cyst	2	0.16	0	0.00
	Alopecia	1	0.08	0	0.00
	Sub-group total	7	0.55	0	0.00
Viral	Verruca	1	0.08	0	0.00
	Wart	1	0.08	0	0.00
	Sub-group total	2	0.16	0	0.00
Fungal	Fungal infection	4	0.31	0	0.00
	Tinea	3	0.23	0	0.00
	Sub-group total	7	0.55	0	0.00
Parasitic	Scabies	1	0.08	0	0.00
	Sub-group total	1	0.08	0	0.00
Venous	Varicose eczema	1	0.08	0	0.00
	Sub-group total	1	0.08	0	0.00
Tumours	Lesion	1	0.08	0	0.00
	Skin nodule	1	0.08	0	0.00
	Naevus	1	0.08	0	0.00
	Sebaceous cyst	1	0.08	3	0.23
	Sub-group total	4	0.31	3	0.23
Nails	Onychomycosis	0	0.00	1	0.08
	Sub-group total	0	0.00	1	0.08
Total		73	5.68	16	1.25

The IMMP report states that 35 skin events were assessed as having a causal relationship, 14 coded as 'probable' and 21 coded as 'possible'.

IMMP identified 29 severe events in the skin group. Of the 29 events, 11 occurred while the patient was taking varenicline or within a month of stopping. IMMP assessed three of the 11 severe events in the skin group as having a causal relationship with varenicline. In addition, two reports of skin eruptions which were likely due to drug hypersensitivity were identified through linkage to NZHIS hospitalisation datasets. In both of these cases, IMMP dispensing data suggested the patient was taking varenicline or had recently stopped. Attempts were made to follow up both these cases with the patient's GP, but it was not possible to determine if varenicline had been considered as a 'possible' suspect medicine.

The five severe cutaneous events considered to have either a causal or unclassifiable relationship with to varenicline are described below.

1. Report F91395 — [redacted] female with a history of [redacted], developed an erythematous, pruritic, raised, confluent rash on the [redacted] day of varenicline, followed by sore throat, chest pain, malaise and anorexia the following day. [redacted] treated with antihistamines and hydrocortisone cream. Varenicline was discontinued as it was the suspect drug. The patient was also taking diclofenac and flucloxacillin. Causality was 'probable'.

2. Report P95206 — [redacted] female was [redacted] chest pain, shortness of breath, sweating, paraesthesia, hallucinations and a facial rash on the [redacted] day of varenicline. Subsequently, varenicline was discontinued as it was suspected to be cause of chest pains. The IMMP report notes that the patient's facial rash could have been part of a generalised anaphylactic/immunological reaction to varenicline as adverse events occurred in several SOCs. Causality was assessed as 'probable'.

3. Report F82182 — [redacted] male [redacted] urticaria, [redacted] days after stopping varenicline. It is unknown if this episode of urticaria was complicated by systemic symptoms. Causality was assessed as 'possible'.

4. Report H89606 — [redacted] male [redacted] generalised skin eruption [redacted] days after stopping varenicline. [redacted] contacted by phone, [redacted] informed us that the drug suspected of causing the above reaction was morphine. However, it was not documented in the case notes that varenicline was excluded as a possible suspect. Therefore, causality with varenicline was 'unclassifiable'.

5. Report H93372 — [redacted] female [redacted] days with a bullous eruption of on her feet after discontinuing varenicline [redacted] weeks ago. Further information also became available on contacting the patient's GP clinic. The aetiology of the eruption was uncertain though a drug hypersensitivity reaction was suspected in this patient who had a history of allergy to several medications [redacted] Again, it was not documented that varenicline was considered as a possible suspect. Therefore, causality with varenicline was 'unclassifiable'.

There were no reports of life-threatening or fatal cutaneous reactions in the skin group dataset.

The New Zealand varenicline data sheet contains the following precaution and adverse events about hypersensitivity reactions.

> ***Precautions>Hypersensitivity reactions***
> *There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with CHAMPIX. Clinical signs included swelling of the face, mouth (tongue, lips and gums), neck (throat and larynx) and extremities. There were rare reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms should discontinue treatment with CHAMPIX and contact a health care provider immediately (see ADVERSE EFFECTS, Post-Marketing Experience).*
>
> *There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using CHAMPIX. As these skin reactions can be life-threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately (see ADVERSE EFFECTS, Post-Marketing Experience).*
>
> ***Adverse Effects>Post-marketing experience***
> *There have also been reports of hypersensitivity reactions, such as angioedema and of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients taking CHAMPIX (see PRECAUTIONS).*

The New Zealand data sheet also lists rash generalised, erythema, pruritus, acne, hyperhidrosis, night sweats as uncommon adverse events that occurred during the clinical trials.

The IMMP report concludes that 35 events were assessed to have a causal relationship with varenicline and there were five reports of severe cutaneous adverse events requiring hospitalisation, three of which were causally linked to varenicline and two which were 'unclassifiable'.

Medsafe comments
The IMMP report mentions that 35 events were assessed as having a causal relationship but no other information on these cases is provided.

The New Zealand data sheet contains a precaution about hypersensitivity reactions and lists rash, erythema, pruritus and acne.

Of the three severe cutaneous events considered to have a causal relationship with to varenicline, one was confounded by diclofenac and flucloxacillin and one occurred over two weeks after stopping varenicline. In the third case, the patient [redacted]

In the recent PSUR for Champix, the sponsor reviewed the safety topic of anaphylactic reactions and cutaneous events and noted no new safety concerns.

3.4.9 Use in Pregnancy

The utilisation and safety of varenicline in pregnancy has been investigated by the IMMP during the monitoring of varenicline because of the scarcity of information on this issue. The varenicline data sheet states that the safety of varenicline in human pregnancy has not been established and that the use of Champix in pregnant women is not recommended.

In IMMP studies, women of reproductive age are defined as women between the ages of 13 and 50 years at the time of first dispensing of the monitored medicine. In this study, these women, for whom exposure to varenicline during pregnancy and/or lactation was a possibility, were identified within the cohort for additional specific follow-up. The prescribing doctors of these women received a supplementary pregnancy/lactation questionnaire in addition to the standard varenicline follow-up questionnaire. Information about the timing of exposure to varenicline during pregnancy and breastfeeding was requested and also information on outcome of the pregnancy.

Linkage to hospital admissions datasets was also performed to identify cases of pregnancy exposure to varenicline that had not been identified from follow-up questionnaires. For those cases which lacked essential information for evaluation, we contacted GPs or other clinic staff for more information and further clarification of dates etc. For all live births identified, national dataset records were checked for each baby in order to identify any adverse outcomes listed in these records.

In the first three years of the IMMP study, pregnancy questionnaires were sent for 3568 women aged 13–50 years old at the time of first dispensing of varenicline. Of the 3568 questionnaires sent, **1387** valid questionnaires were returned.

There were 15 reports of exposure to varenicline during pregnancy identified in the first three years of the study (Table 23). Duration of exposure during pregnancy ranged from a few days to a maximum of four weeks. All women who continued with their pregnancies ceased varenicline on confirmation of pregnancy. Of the 15 reports of exposure to varenicline during pregnancy, there were eight live births.

The New Zealand data sheet for varenicline contains the following information about use of varenicline in pregnancy (1):

> ***Precautions>Use in Pregnancy***
> *Pregnancy Category: B3*
>
> *The safety of varenicline tartrate in human pregnancy has not been established. The use of CHAMPIX in pregnant women is not recommended.*
>
> *There was no evidence of teratogenicity following oral administration of varenicline to rats and rabbits during organogenesis with systemic exposure (plasma AUC) up to 36 times the human plasma AUC at the maximal recommended dose of 1 mg twice daily.*
>
> *In animal reproduction studies, varenicline has been shown to have adverse effects on the foetus and offspring. Oral administration of varenicline to pregnant rabbits during organogenesis resulted in reduced foetal weights at systemic exposure (plasma AUC) 50 times the human plasma AUC at the maximal recommended dose; the no-effect exposure was 23 times the clinical exposure. Oral administration of varenicline to pregnant rats from early gestation until weaning resulted in reduced fertility, increased auditory startle response and decreased rearing in offspring at maternal plasma concentrations 40 times the human plasma Cmax at the maximal recommended dose; the no-effect exposure was 17 times clinical exposure.*
>
> *Women of child bearing potential: Where drug therapy is initiated, treatment should be timed such that the course is completed before conception.*

Table 23: Pregnancy exposure to varenicline in the first three years of the IMMP study

Report No[1]	Age	Dose (mg)	Pregnancy Exposure[2]	Outcome of pregnancy	Outcome for baby	Smoking status
F87427	[redacted]	[redacted]	[redacted]	Termination		Unknown
F87599	[redacted]	[redacted]	[redacted]	Termination		Stopped smoking before varenicline
F87730	[redacted]	[redacted]	[redacted]	Termination		Reduced
F90015	[redacted]	[redacted]	[redacted]	Termination		Did not stop
F87428	[redacted]	[redacted]	[redacted]	Spontaneous abortion at [redacted]		Stopped smoking
H97676	[redacted]	[redacted]	[redacted]	Spontaneous abortion at [redacted]		No info
F91055	[redacted]	[redacted]	[redacted]	Ectopic pregnancy [redacted]		Stopped smoking
F87429	[redacted]	[redacted]	[redacted]	Pre-term delivery at [redacted] weeks	Live birth	Stopped smoking
F87829	[redacted]	[redacted]	[redacted]	Poor fetal growth at [redacted] Delivery at [redacted] weeks	Live birth Feeding difficulties at 2 months of age	Unknown
F85966	[redacted]	[redacted]	[redacted]	Term delivery	Live birth with ankyloglossia	Unknown
F85967	[redacted]	[redacted]	[redacted]	FTND[4]	Live birth with birth asphyxia. Recurrent chest infections	Unknown
F87439	[redacted]	[redacted]	[redacted]	LSCS[5] at term (previous LSCS)	Live birth	Unknown
F96635	[redacted]	[redacted]	[redacted]	[redacted]	Live birth	Unknown
H97677	[redacted]	[redacted]	[redacted]	LSCS at [redacted]	Live birth	No info
H98326	[redacted]	[redacted]	[redacted]	LSCS [redacted] previous LSCS)	Live birth	No info

[1] Prefix in report number denotes source of report
[2] Pregnancy exposure — refers to gestational age of foetus when exposed to varenicline
[3] SP = Starter pack
[4] FTND = Full term normal delivery
[5] LSCS = Lower segment Caesarean section

Pregnancy category B3 is defined as drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

The IMMP report concludes that the case series is too small to suggest or refute any adverse effects of varenicline on the foetus. Smoking is a confounding factor in assessment of all cases of pregnancy exposure in women taking varenicline. Smoking increases the risk of unfavourable pregnancy outcomes in developed countries as it increases the risk of spontaneous abortion, placental complications (abruption and praevia), preterm premature rupture of membranes, preterm delivery, low birth weight, foetal and neonatal death and sudden infant death syndrome. In addition to the complications of maternal smoking on pregnancy, nicotine exposure in pregnancy is known to be injurious to lung development.

The IMMP recommends that Medsafe requests that the sponsor of Champix establishes a pregnancy register for this medicine and undertakes pro-active monitoring or other studies of the use of varenicline during pregnancy.

Medsafe comment
Varenicline treatment is not recommended in pregnancy. The sponsor routinely analyses pregnancy reports in the PSUR. In addition, the sponsor is conducting a prospective population-based cohort study to examine whether varenicline use during pregnancy is associated with an increased risk of major congenital malformations in infants above that associated with smoking during pregnancy. Secondary endpoints include stillbirth, low birth weight, preterm delivery, premature rupture of membranes and sudden infant death syndrome. [redacted]

The study is due to be completed late September 2016.

Medsafe does not consider that any further action is warranted.

4.0 CONCLUSIONS AND RECOMMENDATIONS

Varenicline is a partial α4β2 nicotinic acetylcholine receptor agonist indicated as an aid to smoking cessation (1). A recent Cochrane review found that varenicline increased the chances of successful long-term smoking cessation between two-fold and three-fold compared with pharmacologically unassisted quit attempts (2).

Intensive monitoring of varenicline began in April 2007 and Medsafe directed that the cohort be closed 7 February 2012 with a final report to be supplied 30 June 2012. The IMMP study ran for over four complete years and included 23,721 patients.

PHARMAC began funding varenicline in October 2010. However, the IMMP report did not include any follow-up information of those patients who were dispensed varenicline after the medicine was funded.

The analysis presented in this final IMMP report included dispensing data from the first three or four years of the study. Patient questionnaire responses and adverse event analysis were presented for the first three years of the study. The report did not include patient questionnaire responses and adverse event information for patients who were dispensed the medicine in the fourth year of the study (10,882 patients). At the September 2012 meeting, the MARC recommended that data from the IMMP study and an analysis of the data be provided.

The IMMP has indicated to Medsafe it has completed the clinical assessment of adverse events from the fourth year (April 2010–March 2011) of the study. The IMMP have estimated that the clean-up of this data will be completed mid-2013. Following the clean-up of the data, the data will be analysed. Following requests from Medsafe and the MARC, the IMMP have yet to commit to providing this data to Medsafe.

The IMMP report assessed each drug–event relationship as 'definite', 'probable', 'possible', 'unlikely' or 'unclassified' as defined by the WHO. It is important to note that this assessment does not look to see if there are other likely explanations.

The IMMP study lists the strengths and limitation of the study. An important limitation to consider is that the study does not compare risk of adverse events in patients with other smoking cessation treatment. The IMMP study gives the incidence of adverse events occurring but does not compare these with what the background incidence is in the population and the incidence of the events occurring in smoking cessation without treatment.

Dispensing Analysis

Dispensing analysis was performed on data from the four years of the IMMP study for patient age, sex and ethnicity. Although treatment duration information was collected from the dispensing data from the fourth year no results were included in the IMMP report. From the dispensing data form the first three years it is clear that many patients did not continue the course of treatment for more than two weeks. Treatment duration pre- and post-funding would have been particularly relevant as cost was a reported to be a major factor in not completing the recommended varenicline course.

Questionnaires

A limitation of the IMMP study is the return rate of the questionnaires. Only 40 % of the questionnaires sent regarding patients who were dispensed varenicline were returned to the IMMP. It is also important to note that the majority of the questionnaires were completed by the patients' GP.

The IMMP questionnaire asked doctors to document any past medical history of psychiatric illness, convulsions/seizures, ischaemic heart disease or any other significant history. There were a significant number of reports of patients with a history of psychiatric illness (806 from 4535 responses). The IMMP study report also did not go into any detail as to what the other 1032 significant medical histories mentioned in the questionnaire were.

Hospital linkage data

Linkage to the hospital datasets was not validated in the IMMP study. About 95 % of the adverse events identified were assessed as unlikely to be associated with varenicline use.

Confounders

As this report was written, the IMMP was yet to provide Medsafe with a full line listing that includes important information on confounders for individual cases such as medical history, smoking status of the patient at the time of the adverse event and concomitant medication. In addition, the GP completing the questionnaire may not have listed/known all confounders.

Adverse events general

The top ten adverse events and the top ten clinical groups included all events and were not restricted to those events assessed as having causal relationship with varenicline. 'Nausea', 'depression', 'accidents', 'insomnia', 'headache', 'dreams', 'paroniria', 'vomiting', 'fatigue' and 'neoplasms' were the top ten adverse events identified in the IMMP report. Of note, 'accidents' and 'neoplasm' were not individual adverse events but sub-groups and that all events were included whether a causal relationship was established or not. Of the individual

events in the top ten, all are included in the New Zealand data sheet with the exception of 'paroniria' (nightmare). 'Abnormal dreams' and 'sleep disorder' are listed in the New Zealand data sheet. 'Nightmare' should be included in the New Zealand data sheet.

The IMMP report assessed the specific safety issues of psychiatric adverse events, suicide and suicidal ideation, memory impairment, cardiovascular adverse events, glycaemic control, adverse events in the eye, haematological events, adverse events in the skin and pregnancy.

Psychiatric adverse events

The IMMP report makes reference to withdrawal reactions being identified as an adverse effect of stopping varenicline and that withdrawal reactions are not listed in the New Zealand data sheet. However, the New Zealand data sheet states

> *At the end of treatment, discontinuation of Champix was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3 % of patients. The prescriber should inform the patient accordingly.*

The IMMP claims to have identified and investigated psychotic and aggressive reactions. No data or safety review was provided by the IMMP regarding these topics.

The IMMP recommends that the statement regarding psychiatric events in the New Zealand data sheet be strengthened but did not propose any wording. The New Zealand data sheet contains a significant precaution regarding psychiatric events. The data presented in the IMMP report does not provide evidence to distinguish whether the events were due to varenicline treatment and not due to smoking cessation.

Inclusion of frequency rates of psychiatric adverse events in the New Zealand data sheet cannot be requested until the rates are compared with background rates and confounding factors included in the analysis. This is especially important in the context that 17.8 % of patients reported to have a history of psychiatric illness.

Suicide and suicidal ideation

There was one report of suicide reported while the patient was taking varenicline. However, this report has limited information and it is not known if the patient was actually taking varenicline [redacted]

The IMMP safety review on suicidal ideation concludes that suicidal ideation is causally associated with varenicline treatment and recommends that Medsafe consider whether the data sheet needs to be strengthened. The New Zealand data sheet for varenicline contains a precaution regarding psychiatric symptoms that includes information about the need to monitor patients for neuropsychiatric symptoms and that the patient should stop taking varenicline and contact a healthcare professional immediately if changes in behaviour or thinking, agitation or depressed mood, that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behaviour. Medsafe considers, given the evidence provided in the IMMP report, the current data sheet contains sufficient warning about suicide and suicide ideation.

Memory impairment

The IMMP considers that memory impairment is a new signal and recommends that Medsafe request the sponsor to include memory impairment in the New Zealand data sheet. No information was provided concurrent illness, medical history or smoking status. 'Difficulty concentrating' is listed in the New Zealand data sheet as an expected event following smoking cessation.

This potential safety topic has already been identified by the sponsors who currently review this concern in their PSUR. In the recent PSUR, the sponsor noted no new safety concerns.

The IMMP report has not provided sufficient information regarding the reports of memory impairment to warrant any changes to the New Zealand data sheet at this time. IMMP should review their data to identify any possible risk factors or interactions that might be pertinent to memory impairment.

Cardiovascular events

Cardiovascular events are expected in smokers and it is possible that many patients were trying to give up smoking because they had cardiovascular disease. Following the recommendation of the MARC at the September 2011 meeting, the New Zealand data sheet was updated to include information about reports of cardiovascular related adverse events associated with the use of varenicline. No further information was provided in the IMMP report than that presented to the MARC at the September 2011 meeting. The sponsor is currently conducting a safety review with cardiovascular events as a primary outcome. Both the IMMP and Medsafe consider that until there is more evidence available (ie, following the results of the 'CAT' study) no changes are warranted. At the September 2012 meeting, the MARC requested Medsafe review the results of the 'CAT' study when they are published.

Glycaemia control

The IMMP report recommended the New Zealand data sheet be updated to state there have been post-marketing reports of new-onset altered glycaemic control in non-diabetic patients taking varenicline. The majority of the cases new-onset cases of altered glycaemic control that occurred while the patient was taking varenicline had a negative dechallenge. Increased appetite is associated with smoking cessation and nicotine withdrawal, and this change in dietary behaviour can affect glycaemic control. The New Zealand data sheet currently contains information about the physiological changes resulting from smoking cessation and lists glycosuria as an uncommon adverse effect. Medsafe considers that no changes to the current New Zealand data sheet regarding new-onset altered glycaemic control are warranted at this time.

Adverse events in the eye

The IMMP identified six reports of blurred vision and two reports of abnormal vision. The IMMP recommend Medsafe should request the sponsor to include blurred vision and visual disturbance in the New Zealand data sheet. The IMMP assessed five of the reports as having a causal relationship with varenicline. However, the many of these reports are confounded by concomitant medications and concurrent illness. Many of the concomitant medications have blurred vision or glaucoma listed as an adverse event in the New Zealand data sheet. These include pantoprazole, clonazepam, ranitidine and symbicort.

The New Zealand data sheet currently lists scotoma, scleral discolouration, eye pain, mydriasis, myopia, photophobia and lacrimation increased. Medsafe considers that given the evidence in presented in the IMMP report, no changes to the New Zealand data sheet are necessary at the current time.

Haematological events

The IMMP recommended that epistaxis and gingival bleeding should be included in the varenicline data sheet. The IMMP identified one report of bleeding (bowel), two reports of bleeding (gums) and two reports of epistaxis while the patient was taking varenicline. Of these cases, one patient reported with bleeding (gums) was also on warfarin and the case of bleeding (bowel) was assessed as unlikely to be associated with varenicline. No further details were included in the IMMP report regarding the other reports. In particular, no information regarding concomitant medications, medical history, concurrent illness or smoking status was included.

The sponsor identified several lines of evidence against the IMMP proposed mechanism for increased bleeding. In addition, smoking cessation itself is a confounder as it has the potential to increase the likelihood of bleeding. The New Zealand data sheet currently mentions there have been post-marketing reports of haemorrhagic events in patients taking Champix. On the evidence provided in the IMMP report, Medsafe consider no changes to the data sheet are required at present.

Adverse events in the skin

The IMMP report describes five reports of severe cutaneous events. Of the three events, two were considered by the IMMP as unclassifiable. Of the three remaining severe cutaneous events considered to have a causal relationship with varenicline, one was confounded by concomitant medication and one occurred over two weeks after stopping varenicline. In the third case, [redacted]. The IMMP not in the recommendations that further follow-up of the two unclassifiable cases is still required.

Further monitoring or additional studies are recommended by the IMMP. The IMMP suggests that the IMMP could examine skin events in the four year cohort. Medsafe and the MARC have requested the data from the fourth year of the IMMP study and have yet to be provided with this data.

In the latest PSUR, anaphylactic reaction and cutaneous events were reviewed but not discussed as no new safety concerns were identified.

Use in pregnancy

Varenicline treatment is not recommended in pregnancy. The New Zealand data sheet currently states the safety of varenicline in human pregnancy has not been established (1). The IMMP report recommended that Medsafe request the sponsor to establish a pregnancy register for this medicine and that further monitoring should be undertaken.

The sponsor routinely assesses pregnancy reports in the Champix PSUR. In addition, the sponsor is currently conducting a varenicline pregnancy cohort study. The results of this study are expected in 2016. Until the results of the pregnancy cohort are complete or any safety issues are noted in the PSURs, Medsafe considers no further action on this issue is necessarily at this time.

Effectiveness of varenicline

The IMMP state that the effectiveness of varenicline in real-life clinical use may not be as good as promoted by the sponsor and further studies should be requested. However, as noted by the IMMP, effectiveness was not a primary outcome of the study.

The percentage of patients that successfully quit smoking identified by the IMMP was determined as 28.7 % of patients who had a valid questionnaire returned. However, smoking status was unknown in 33.5 % of the patients. In addition, the percentage of valid questionnaire returned was less that 40 %.

During clinical trials, the continuous quit rate was determined to be approximately 40 % at four weeks and approximately 25 % at week 52 (1). A 2012 Cochrane review found that varenicline increased the chances of successful long-term smoking cessation between two- and threefold compared with pharmacologically unassisted quit attempts (2).

Medsafe considers that as the sponsor is currently undertaking numerous studies, no further studies should be requested from the sponsor.

Risk Management Plan for varenicline

The sponsor has provided Medsafe with the latest Risk Management Plan for varenicline. A summary table of the Risk Management Plan is included in Annex 12. The potential risks being monitored include neuropsychiatric symptoms, myocardial infarction, suicide/suicidal ideation, seizures, very elderly, cardiovascular disease, COPD, psychosis, depression, pregnancy/lactation, adolescents and overdose.

Current safety studies underway or planned by the sponsor of varenicline

The sponsor is currently conducting or planning safety studies on the use of varenicline (Annex 13). These studies include varenicline use in healthy adolescent smokers, pregnancy and patients with a history of psychiatric disorders. In addition, cardiovascular safety assessments are being included in the study on patients with a history of psychiatric disorders.

Dissemination of the IMMP study

Medsafe proposes publishing the IMMP report, along with Medsafe's assessment report and the MARC minutes, on the Medsafe website. In addition, a summary of the IMMP report could be published in *Prescriber Update.*

Overall Summary

'Nightmare' is the only adverse event in the top ten adverse events in the IMMP study currently not included in the New Zealand data sheet. The sponsor should be contacted and requested to include 'nightmare' in the New Zealand data sheet.

The sponsor is current conducting four varenicline safety studies. The data from the sponsor's safety studies will be reviewed by Medsafe and taken to the MARC if any new safety issues are identified.

Medsafe considers that there is insufficient data and evidence provided in the IMMP report to warrant any further regulatory action.

The benefit-risk of varenicline remains positive.

5.0 REFERENCES

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6.0 ANNEXES

1. Varenicline tartrate IMMP revised report — January 2013 version
2. Varenicline tartrate IMMP new Annex 3: List of events for varenicline patients in the first three years of the IMMP study
3. Varenicline tartrate IMMP new Annex 4: List of reports for varenicline patients in the first three years of the IMMP study
4. Varenicline tartrate IMMP new Annex 5: List of events for varenicline patients in the first three years of the IMMP study identified from patient NHI records
5. Varenicline tartrate IMMP new Annex 6: Expanded tables to separate on-medicine and off-medicine events
6. Varenicline tartrate IMMP revised Annex 4: At the time of writing not yet received
7. Pfizer New Zealand Ltd. 2012. Champix data sheet. 4 May 2012
8. WHO-UMC Causality Categories
9. A phase 4 12-week, double-blind, placebo-controlled, multicentre study evaluating the safety and efficacy of varenicline tartrate (CP-526,555) 1 mg BID for smoking cessation in subject with depression
10. Tan M, Harrison-Woolrych M. 2012. Memory impairment associated with varenicline: A case series from the New Zealand Intensive Medicines Monitoring Programme. *European Journal of Clinical Pharmacology*
11. Cardiovascular safety of varenicline: meta-analysis of varenicline randomized, blinded, controlled clinical trials with treatment duration of 12 weeks or longer
12. Summary of the Risk Management Plan for varenicline
13. Summary of varenicline safety studies

DATA SHEET

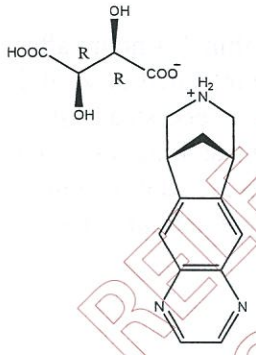
CHAMPIX®
(varenicline as tartrate)

PRODUCT NAME

CHAMPIX® 0.5 mg and 1 mg film-coated tablets.

DESCRIPTION

Varenicline tartrate powder is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. The pKa (ionisation constant) for varenicline is 9.2. The octanol-water partition coefficient (Log D) of varenicline tartrate is -1.23 at pH 5, -0.817 at pH 7 and 0.758 at pH 9. Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of $C_{13}H_{13}N_3 \bullet C_4H_6O_6$. The chemical structure is:



CAS No: 375815-87-5

CHAMPIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side. Each film-coated tablet of varenicline contains the appropriate amount of varenicline as the tartrate salt and the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate anhydrous, croscarmellose sodium, silica – colloidal anhydrous, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Drugs used in nicotine dependence, ATC code: *N07BA*.

Varenicline is a partial agonist activity at α4β2 neuronal nicotinic acetylcholine receptors where it binds with high affinity and selectivity to produce an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in blockade of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity).

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to the α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity. The maximal activity of varenicline was approximately 30-50% that of nicotine *in vitro* and approximately 30% that of nicotine *in vivo*. Varenicline blocks the ability of nicotine to activate the α4β2 receptor and thus to stimulate the central nervous mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds with higher affinity to the α4β2 receptor subtype than to other common nicotinic receptors (>500-fold α3β4, >3,500-fold α7, >20,000-fold α1βγδ), or to non-nicotinic receptors and transporters (>2,000-fold).

Pharmacokinetics

Absorption

Maximum plasma concentrations of varenicline tartrate occur typically within 3-4 hours after oral administration. Mean (SD) C_{max} was 9.22 (2.05) ng/mL at the recommended dose of 1 mg BID. Following administration of multiple oral doses to healthy volunteers, steady-state conditions were reached within 4 days. Varenicline tartrate exhibits linear kinetics when given as single or repeated doses. Absorption is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline tartrate is unaffected by food or time-of-day dosing.

Distribution

Plasma protein binding of varenicline tartrate is low (<20%) and independent of both age and renal function. Apparent volume of distribution averaged 415 litres (%CV=50) at steady-state.

Metabolism

Varenicline tartrate undergoes minimal metabolism with 92% eliminated unchanged in the urine.

Elimination

The elimination half-life of varenicline tartrate is approximately 24 hours (individual range 10-58 hr). Renal elimination of varenicline tartrate is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2.

Pharmacokinetics in Special Patient Populations

There are no clinically meaningful differences in varenicline tartrate pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Patients with Hepatic Impairment

Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic insufficiency and the potential for clinically meaningful drug interactions between varenicline and metabolic inhibitors/inducers is low.

Renal Impairment

Varenicline tartrate pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50ml/min and ≤80ml/min); in patients with moderate renal impairment (estimated creatinine clearance ≥30ml/min and ≤50ml/min), varenicline tartrate exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80ml/min). In subjects with severe renal impairment (estimated creatinine clearance <30ml/min), varenicline tartrate exposure increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline tartrate was efficiently removed by haemodialysis. While no dosing adjustment is necessary for patients with mild to moderate renal impairment, a reduced dosing frequency of 1 mg once daily is recommended for patients with severe renal impairment (see **DOSAGE AND ADMINISTRATION**). Dosing should begin at 0.5 mg once daily for the first 3 days, and then increased to 1 mg once daily.

Elderly (> 65 years)

No dosage adjustment is necessary for elderly patients (see **DOSAGE AND ADMINISTRATION**).

A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1mg varenicline tartrate given once or twice daily to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects.

Children and Adolescents

Because the safety and effectiveness of varenicline tartrate in paediatric patients have not been established, varenicline is not recommended for use in patients under 18 years of age.

Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric subjects aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight >55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When a 0.5 mg dose was given twice a day, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that seen in the adult population.[†]

CLINICAL TRIALS

The efficacy of CHAMPIX in smoking cessation was demonstrated in three pre-marketing clinical trials in which a total of 2619 chronic cigarette smokers (≥10 cigarettes per day) received varenicline. Two of these studies were double-blind comparisons between varenicline, bupropion and placebo, assessing critical aspects of smoking cessation, including end-of-treatment and long-term abstinence rates after 12 weeks of treatment. In addition, the effects on reducing craving and withdrawal that can occur during smoking cessation and the reinforcing effects that can perpetuate smoking behaviour were studied. The third study assessed the effect of an additional 12 weeks of treatment on maintaining long-term abstinence.

Comparative Clinical Studies

Two identical double-blind clinical trials prospectively compared the efficacy of CHAMPIX (1 mg twice daily), sustained release bupropion (150 mg twice daily) and placebo in smoking cessation. Patients were treated for 12 weeks and then were followed up for a total study duration of 52 weeks. The CHAMPIX dosage of 1 mg twice daily was achieved using a titration of 0.5 mg once daily for the initial 3 days followed by 0.5 mg twice daily for the next 4 days. The bupropion dosage of 150 mg twice daily was achieved using a 3-day titration of 150 mg once daily. Patients set a date to stop smoking (target quit date, TQD) with dosing starting 1-2 weeks before this date.

The primary endpoint of the two studies was the carbon monoxide (CO) confirmed, 4-week continuous quit rate (4W-CQR) from week 9 through week 12. The quit rates are the proportions of all patients treated (i.e., intent-to-treat analysis) who abstained from smoking. The primary endpoint for CHAMPIX demonstrated statistical superiority to bupropion and placebo. Key secondary endpoints for both studies were Continuous Abstinence (CA) from weeks 9-52 and the Long Term Quit Rate (LTQR) at week 52. CA was defined as the proportion of all subjects who did not smoke (not even a puff of a cigarette) from week 9 through week 52 and had an exhaled CO measurement of >10ppm. LTQR was defined as the proportion of all subjects treated who were responders for the primary endpoint in the treatment phase and had no more than 6 days of cigarette smoking during the non-treatment phase.

In both studies the CO-confirmed 4-week CQR for week 9 through week 12 was superior ($p<0.0001$) for patients given CHAMPIX compared with the placebo and bupropion groups. Based on this endpoint, the odds of stopping on CHAMPIX were 3.91 (95% CI: 2.74, 5.59) and 3.85 (2.69, 5.50) times those of stopping on placebo in Studies 1 and 2 respectively; the odds of stopping on CHAMPIX were 1.96 (1.42, 2.72) to 1.89 (1.37, 2.61) times those of stopping on bupropion.

The 4W-CQR (weeks 9-12), and CA (weeks 9-52) and LTQR (week 52) from Studies 1 and 2 are included in the following table:

Table 1 Continuous Quit Rates, Continuous Abstinence and Long Term Quit Rates for Studies 1 and 2

	Study 1 n=1022			Study 2 n=1023		
	4W CQR	**CA wk 9-52**	**LTQR wk 52**	**4W CQR**	**CA wk 9-52**	**LTQR wk 52**
CHAMPIX	44.4%[a]	22.1%[b]	25.5%[c]	44.0%[a]	23.0%[d]	25.4%[e]
Bupropion	29.5%	16.4%	17.9%	30.0%	15.0%	18.2%
Placebo	17.7%	8.4%	9.6%	17.7%	10.3%	12.6%

[a] p <0.0001 vs. placebo and bupropion
[b] p <0.0001 vs. placebo, p=0.0640 vs. bupropion
[c] p <0.0001 vs. placebo, p=0.0161 vs. bupropion
[d] p <0.0001 vs. placebo, p=0.0062 vs. bupropion
[e] p <0.0001 vs. placebo, p=0.0205 vs. bupropion

Based on the key secondary endpoint of carbon monoxide confirmed (not even a puff of a cigarette) Continuous Abstinence from week 9 through week 52 (CA weeks 9-52), the odds of stopping on CHAMPIX were 2.66 (95% CI: 1.72, 4.11) and 3.13 (1.97, 4.97) times those of stopping on placebo in Studies 1 and 2 respectively.

For the LTQR at 52 weeks the odds of stopping smoking on CHAMPIX were 3.30 (2.13, 5.11) and 2.40 (1.60, 3.60) times those of stopping on placebo in Studies 1 and 2, respectively.

In Studies 1 and 2, three aspects of smoking cessation were investigated using validated Patient Reported Outcomes questionnaires: Craving, measured by Brief Questionnaire of Smoking Urges (QSU-Brief) and Minnesota Nicotine Withdrawal Scale (MNWS) Urge to Smoke item; Withdrawal, measured by 4 MNWS subscales; and Reinforcing Effects of Smoking, measured by five Modified Cigarette Evaluation Questionnaire (mCEQ) subscales.

Patient Reported Craving, Withdrawal and Reinforcing Effects Of Smoking

Across both Studies 1 and 2, craving and withdrawal were significantly reduced in patients randomized to CHAMPIX in comparison with placebo. CHAMPIX also significantly reduced reinforcing effects of smoking that can perpetuate smoking behaviour in patients who smoke during treatment compared with placebo.

Maintenance of Abstinence Study

The third study assessed the benefit of an additional 12 weeks of CHAMPIX therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label CHAMPIX 1 mg twice daily for 12 weeks. Patients who stopped smoking by week 12 were then randomised to receive either CHAMPIX (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks.

The primary study endpoint was the CO-confirmed continuous abstinence rate from week 13 through week 24 in the double-blind treatment phase. The two key secondary endpoints were

the continuous abstinence (CA) rate for week 13 through week 52 and the long-term quit rate (LTQR) at week 52. The key results are summarised in the following table:

Table 2 Continuous Abstinence and Long Term Quite Rates for Maintenance of Abstinence Study

	CHAMPIX n=602	Placebo n=604
CA wk 13-24	70.6%*	49.8%
CA wk 13-52	44.0%**	37.1%
LTQR at week 52	47.8%***	40.7%

*p<0.0001 vs placebo, **p=0.0126 vs placebo, ***p=0.0119 vs placebo

This study showed the benefit of an additional 12-week treatment with CHAMPIX 1 mg twice daily for the maintenance of smoking cessation compared to placebo. The odds of maintained abstinence at week 24, following an additional 12 weeks of treatment with CHAMPIX, were 2.47 times those for placebo (95% CI: 1.95, 3.15). Superiority to placebo for continuous abstinence was maintained through week 52 (Odds Ratio = 1.35, 95% CI: 1.07, 1.70).

Study in Subjects with Cardiovascular Disease

Varenicline was evaluated in a randomised, double-blind, placebo-controlled study of 703 subjects with stable, documented cardiovascular disease (other than or in addition to hypertension) that had been diagnosed for more than 2 months. Subjects aged 35 to 75 years were randomised to varenicline 1 mg twice a day or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47.3 %) compared to subjects treated with placebo (14.3%) (odds ratio 6.05; 95% CI 4.13, 8.86; p<0.0001) and from week 9 through 52 (19.8%) compared to subjects treated with placebo (7.4%) (odds ratio 3.19; 95% CI 1.97, 5.18; p<0.0001). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment-emergent and non-treatment-emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency ≥ 1% in either treatment group: nonfatal myocardial infarction (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs 1.1%). During non-treatment follow up to 52 weeks, adjudicated events with a frequency ≥1% included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina. cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52 week study. The key results are summarized in the following table†:

Table 3 Rates of CO-confirmed abstinence for Study in Subjects with Cardiovascular Disease†			
	Varenicline n=353	Placebo n=350	Odds ratio (95% CI), p value
CA wk 9-12	47.3%	14.3%	6.05 (4.13, 8.86) p<0.0001
CA wk 9-52	19.8%	7.4%	3.19 (1.97, 5.18) p<0.0001

Study in Subjects with Chronic Obstructive Pulmonary Disease

Varenicline was evaluated in a randomised, double-blind, placebo-controlled study of 499 subjects with mild-to-moderate chronic obstructive pulmonary disease with post-bronchodilator FEV1/FVC <70% and FEV1 ≥ 50% of predicted normal value. Subjects aged ≥ 35 years were randomised to varenicline 1 mg twice a day or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (42.3%) compared to subjects treated with placebo (8.8%) (odds ratio 8.40; 95% CI 4.99, 14.14; p<0.0001) and from week 9 through 52 (18.6%) compared to subjects treated with placebo (5.6%) (odds ratio 4.04; 95% CI 2.13, 7.67; p<0.0001). Adverse events in this study were quantitatively and qualitatively similar to those observed in premarketing studies. The key results are summarized in the following table†:

Table 4 Rates of CO-confirmed abstinence for Study in Subjects with Obstructive Pulmonary Disease†			
	Varenicline n=248	Placebo n=251	Odds ratio (95% CI), p value
CA wk 9-12	42.3%	8.8%	8.40 (4.99, 14.14) p<0.0001
CA wk 9-52	18.6%	5.6%	4.04 (2.13, 7.67) p<0.0001

Flexibility in Setting a Quit Date

The effect of varenicline 1 mg twice a day in a flexible, patient-selected quit date setting was assessed in a double-blind, placebo-controlled study of 651 subjects. Subjects were randomised 3:1 to varenicline or placebo for a treatment of 12 weeks and a followed up post-treatment for another 12 weeks. In this study, 486 subjects received varenicline and 165 received placebo. Subjects were instructed to select a quit date after the initial week of dose titration and before the clinical visit at the end of week 5 of treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (53.94%) compared to patients treated with placebo (19.4%) (odds ratio 6.03; 95% CI 3.80, 9.56; p<0.0001) and from week 9 through 24 (35.2%) compared to subjects treated with placebo (12.73%) (odds ratio 4.45; 95% CI 2.62, 7.55; p<0.0001). Adverse events in this study were quantitatively and qualitatively similar to those observed in premarketing studies. The key results are summarized in the following table†:

Table 5 Rates of CO-confirmed abstinence for Flexibility in Setting a Quit Date Study†			
	Varenicline n=486	Placebo n=165	Odds ratio (95% CI), p value
CA wk 9-12	53.9%	19.4%	6.03 (3.80, 9.56) p<0.0001
CA wk 9-24	35.2%	12.7%	4.45 (2.62, 7.55) p<0.0001

INDICATIONS

CHAMPIX is indicated as an aid to smoking cessation.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

Effects of Smoking Cessation

Physiological changes resulting from smoking cessation, with or without treatment with CHAMPIX, may alter pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.

Smoking cessation, with or without pharmacotherapy, has been associated with the exacerbation of underlying psychiatric illness (e.g. depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

There is no clinical experience with CHAMPIX in patients with epilepsy.

At the end of treatment, discontinuation of Champix was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients. The prescriber should inform the patient accordingly.

Psychiatric Symptoms

Serious neuropsychiatric symptoms have occurred in patients being treated with CHAMPIX. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking; however, some of these symptoms have occurred in patients who continued to smoke. Although a causal association between CHAMPIX and these symptoms

has not been established, in some reports the association cannot be excluded. Patients being treated with CHAMPIX and their families, should be alerted to the need to monitor for neuropsychiatric symptoms including changes in behaviour or thinking, anxiety, psychosis, mood swings, agitation, aggression, depressed mood, suicidal ideation and suicidal behaviour. Doctors should discuss the efficacy and safety profile of CHAMPIX with patients attempting to quit smoking with CHAMPIX and advise them of the possible emergence of neuropsychiatric symptoms. These symptoms, as well as worsening of pre-existing psychiatric illness, have been reported in patients attempting to quit smoking while taking CHAMPIX in the post-marketing experience. Patients and their families, should be advised that the patient should stop taking CHAMPIX and contact a health care professional immediately if changes in behaviour or thinking, agitation or depressed mood, that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behaviour In many post-marketing cases, resolution of symptoms after discontinuation of CHAMPIX was reported, although in some cases the symptoms persisted; therefore, ongoing follow up should be provided until symptoms resolve. Patients and their families should be encouraged to report any history of psychiatric illness prior to initiating treatment. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHAMPIX and the safety and efficacy of CHAMPIX in such patients has not been established.

Hypersensitivity Reactions

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with CHAMPIX. Clinical signs included swelling of the face, mouth (tongue, lips and gums), neck (throat and larynx) and extremities. There were rare reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms should discontinue treatment with CHAMPIX and contact a health care provider immediately (see **ADVERSE EFFECTS, Post-Marketing Experience**).

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using CHAMPIX. As these skin reactions can be life-threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately (see **ADVERSE EFFECTS, Post-Marketing Experience**).

Cardiovascular Events

In a single smoking cessation trial of patients with stable cardiovascular disease, while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with varenicline. No causal relationship between these events and varenicline has been established. Smoking is an independent and major risk factor for cardiovascular disease. (See CLINICAL TRIALS – Study in Subjects with Cardiovascular Disease).†

Effects on Ability to Drive and Use Machines

Patients should be advised to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them.

Effects on Fertility

It is not expected that varenicline tartrate would impair fertility. Varenicline did not impair fertility in rats at oral doses producing plasma concentrations up to 40 times the human plasma C_{max} at the maximal recommended dose of 1 mg twice daily (see **Use in Pregnancy).**

Use in Pregnancy

Pregnancy Category: B3

The safety of varenicline tartrate in human pregnancy has not been established. The use of CHAMPIX in pregnant women is not recommended.

There was no evidence of teratogenicity following oral administration of varenicline to rats and rabbits during organogenesis with systemic exposure (plasma AUC) up to 36 times the human plasma AUC at the maximal recommended dose of 1 mg twice daily.

In animal reproduction studies, varenicline has been shown to have adverse effects on the foetus and offspring. Oral administration of varenicline to pregnant rabbits during organogenesis resulted in reduced foetal weights at systemic exposure (plasma AUC) 50 times the human plasma AUC at the maximal recommended dose; the no-effect exposure was 23 times the clinical exposure. Oral administration of varenicline to pregnant rats from early gestation until weaning resulted in reduced fertility, increased auditory startle response and decreased rearing in offspring at maternal plasma concentrations 40 times the human plasma C_{max} at the maximal recommended dose; the no-effect exposure was 17 times clinical exposure.

Women of child bearing potential: Where drug therapy is initiated, treatment should be timed such that the course is completed before conception.

Use in Lactation

It is not known whether varenicline is excreted in human milk. Because many drugs are excreted in human milk and because the potential for adverse effects in nursing infants from CHAMPIX is unknown, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Carcinogenicity

Carcinogenicity studies were performed in mice and rats at respective oral doses of varenicline up to 20 mg/kg/day and 15 mg/kg/day for 2 years, with respective systemic drug exposure (C_{max}) up to 130 and 50 times the human plasma C_{max} at the maximal recommended dose of 1 mg twice daily. There was no evidence of carcinogenicity in mice or female rats. Male rats showed increased incidences of hibernoma (a rare tumour of brown fat) at systemic exposures of 25 times the human C_{max} (incidence 1/65 rats) and 50 times the human C_{max}

(incidence 2/65 rats); the no-effect exposure was 10 times the human C_{max}. The clinical relevance of this finding has not been established.

Genotoxicity

Varenicline had no genotoxic effects, with or without metabolic activation, based on the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

INTERACTIONS WITH OTHER MEDICINES

Based on varenicline characteristics and clinical experience to date, varenicline has no known clinically meaningful drug interactions. No dosage adjustment of varenicline or co-administered drugs listed below is recommended.

In vitro studies demonstrate that varenicline tartrate does not inhibit cytochrome P450 enzymes (IC_{50}> 6,400 ng/mL). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline was shown not to induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline tartrate is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

In vitro studies demonstrate that varenicline tartrate does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g. metformin – see below) are unlikely to be affected by varenicline tartrate.

In vitro studies demonstrate that active renal secretion of varenicline tartrate is mediated by the human organic cation transporter, OCT2. Co-administration with inhibitors of OCT2 does not require a dose adjustment of varenicline as the increase in systemic exposure to varenicline tartrate is not expected to be clinically meaningful (see cimetidine interaction below). Furthermore since metabolism of varenicline tartrate contributes to less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline tartrate (see **Pharmacokinetics**) and therefore a dose adjustment of CHAMPIX would not be required.

Metformin: Varenicline tartrate (1 mg twice daily) did not affect the pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine: Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided.

Digoxin: Varenicline tartrate (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose.

Warfarin: Varenicline tartrate (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R,S)-warfarin. Prothrombin time (INR) was not affected by varenicline tartrate. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see **PRECAUTIONS**).

Use with other therapies for smoking cessation:

Bupropion: Varenicline tartrate (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily).

Nicotine replacement therapy (NRT): When varenicline (1 mg twice daily) and nicotine replacement therapy (transdermal 21 mg/day) were co-administered to smokers (N=24) for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dyspepsia, fatigue and dizziness was greater for the combination than for NRT alone.

Safety and efficacy of CHAMPIX in combination with other smoking cessation therapies have not been studied.

ADVERSE EFFECTS

Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood; insomnia, irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain have been reported in patients attempting to stop smoking. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse effects associated with study drug treatment or those possibly associated with nicotine withdrawal.

Clinical trials included approximately 4,000 patients treated with CHAMPIX for up to 1 year (average exposure 84 days). In general, where adverse events occurred, onset was in the first week of therapy; severity was generally mild to moderate and there were no differences by age, race or gender with regard to the incidence of adverse effects.

The treatment discontinuation rate was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse events in varenicline treated patients were as follows: nausea (2.7% vs 0.6% placebo), headache (0.6% vs 1.0% for placebo), insomnia (1.3% vs 1.2% for placebo), and abnormal dreams (0.2% vs 0.2% for placebo)

Table 3 includes the most frequently occurring events (at a rate of ≥1% and an incidence higher than that for placebo). These data are derived from a pooled database of studies in which patients were randomised to receive 12 weeks of treatment using the recommended dosage regimen.

Table 6 Adverse Events considered treatment-related and reported in studies at a rate ≥1% and at an incidence higher than placebo, conducted using the recommended dosage regimen

	Percentage of Patients Reporting Event	
	CHAMPIX N=821	**Placebo N=805**
Gastrointestinal Disorders		
Nausea	28.6	8.8
Constipation	5.8	2.2
Flatulence	5.1	2.5
Dry mouth	5.6	4.1
Dyspepsia	3.8	1.5
Vomiting	4.1	0.7
Abdominal Distension	1.3	0.4
Stomach Discomfort	1.1	0.5
General Disorders and Administration Site Conditions		
Fatigue	4.6	3.9
Metabolism and Nutrition Disorders		
Increased Appetite	1.7	1.2
Nervous System Disorders		
Headache	10.1	8.4
Dizziness	5.2	4.6
Dysgeusia	5.0	3.6
Somnolence	3.0	2.1
Psychiatric Disorders		
Insomnia	13.8	10.6
Abnormal Dreams	12.4	4.5
Sleep Disorder	4.8	2.9

In the listings below all adverse effects, which occurred at a rate lower than 1% and greater than placebo are listed by system organ class and frequency (uncommon (≥1/1,000, <1/100)).

System Organ Class **Adverse Drug Effects**

Infections and Infestations

Uncommon Bronchitis, nasopharyngitis, sinusitis, fungal infection, viral infection

Metabolism and Nutrition Disorders

Uncommon Anorexia, decreased appetite, polydipsia

Psychiatric Disorders

Uncommon Panic reaction, bradyphrenia, thinking abnormal, mood swings

Nervous System Disorders

Uncommon Tremor, coordination abnormal, dysarthria, hypertonia, restlessness, dysphoria, hypoaesthesia, hypogeusia, lethargy, libido increased, libido decreased

Cardiac Disorders

Uncommon Atrial fibrillation, palpitations

Vascular Disorders

Uncommon Hot flush, varicose vein

Eye Disorders

Uncommon Scotoma, scleral discolouration, eye pain, mydriasis, photophobia, myopia, lacrimation increased

Ear and Labyrinth Disorders

Uncommon Tinnitus

Respiratory, Thoracic and Mediastinal Disorders

Uncommon Dyspnoea, cough, hoarseness, pharyngolaryngeal pain, throat irritation, respiratory tract congestion, sinus congestion, post nasal drip, rhinorrhoea, snoring

Gastrointestinal Disorders

Uncommon Haematemesis, haematochezia, gastritis, gastrooesophageal reflux disease, abdominal pain, change of bowel habit, salivary hypersecretion, abnormal faeces, eructation, aphthous stomatitis, gingival pain, tongue coated

Skin and Subcutaneous Tissue Disorders

Uncommon Rash generalised, erythema, pruritus, acne, hyperhidrosis, night sweats

Musculoskeletal and Connective Tissue Disorders

Uncommon Joint stiffness, muscle spasms, chest wall pain, costochondritis

Renal and Urinary Disorders

Uncommon Glycosuria, nocturia, polyuria

Reproductive System and Breast Disorders

Uncommon Menorrhagia, vaginal discharge, sexual dysfunction

General Disorders and Administration Site Conditions

Uncommon Chest discomfort, chest pain, pyrexia, feeling cold, asthenia, circadian rhythm sleep disorder, malaise, cyst

Investigations

Uncommon Blood pressure increased, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, heart rate increased, liver function test abnormal, platelet count decreased, weight increased, semen abnormal, C-reactive protein increased, blood calcium decreased

Post-Marketing Experience

The following adverse events have been reported during post-approval use of CHAMPIX. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of neuropsychiatric symptoms such as depressed mood, agitation, hallucinations, changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour suicidal ideation and suicide in patients attempting to quit smoking while taking CHAMPIX. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of CHAMPIX in these reports is not known (see **PRECAUTIONS**).

There have also been reports of hypersensitivity reactions, such as angioedema and of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients taking CHAMPIX (see **PRECAUTIONS**).

There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischaemic and haemorrhagic events in patients taking CHAMPIX. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.

DOSAGE AND ADMINISTRATION

Use in Adults

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support.

The recommended dose of CHAMPIX is 1 mg twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg one daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of Treatment:	1 mg twice daily

The patient should set a date to stop smoking. CHAMPIX dosing should start 1 – 2 weeks before this date. Alternatively, a flexible approach to quitting smoking may be adopted. Patients can begin varenicline dosing and then quit smoking between days 8 and 35 of treatment (see CLINICAL TRIALS, Flexibility in Setting a Quit Date).†

CHAMPIX tablets should be swallowed whole with water. CHAMPIX can be taken with or without food.

Patients should be treated with CHAMPIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX at 1 mg twice daily is recommended to further increase the likelihood of long-term abstinence.

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Dose tapering of CHAMPIX is not required at the end of treatment.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with mild to moderate renal impairment.

For patients with severe renal impairment, the recommended dose of CHAMPIX is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily (see **Pharmacokinetics**)

Based on insufficient clinical experience with Champix in patients with end stage renal disease, treatment is not recommended in this patient population (see **Pharmacokinetics**, ***Pharmacokinetics in Special Patient Populations***).

Use in Patients with Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment (see **Pharmacokinetics**)

Use in the Elderly

No dosage adjustment is necessary for elderly patients (see **Pharmacokinetics**). Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient.

Use in Children

Safety and effectiveness of CHAMPIX in paediatric patients have not been established; therefore, CHAMPIX is not recommended for use in patients under 18 years of age (see **Pharmacokinetics**).

OVERDOSAGE

No cases of overdose were reported in pre-marketing clinical trials.

In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease (see **Pharmacokinetics**), however, there is no experience in dialysis following overdose.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Aclar / PVC / blisters with aluminium foil backing in an initial dosing pack containing one blister of 11 x 0.5 mg film-coated tablets and a second blister of 14 x 1 mg film-coated tablets in a carton or a heat sealed wallet.

Aclar / PVC blisters with aluminium foil backing in a pack containing 28 or 56 x 1 mg film-coated tablets in a carton or secondary heat sealed wallet.

High-density polyethylene (HDPE) bottle with polypropylene child resistant closure and an aluminium foil/polyethylene induction seal containing 56 x 1 mg film-coated tablets (Not currently marketed in New Zealand).

Shelf Life: 2 years when stored below 30°C

NAME AND ADDRESS OF THE SPONSOR

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MEDICINE CLASSIFICATION

Prescription Medicine

CHAMPIX is being monitored on the New Zealand Intensive Medicines Monitoring Program (IMMP).

DATE OF PREPARATION

04 May 2012

† Please note change to Data Sheet.

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