Champix

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0070/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any	11/04/2018		Annex II, Labelling and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				

	B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur. B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IB/0069/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	12/01/2018		SmPC, Labelling and PL	
PSUSA/3099/ 201705	Periodic Safety Update EU Single assessment - varenicline	11/01/2018	n/a		PRAC Recommendation - maintenance
IB/0067/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	13/07/2017	n/a		

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.c.1.z - Change in immediate packaging of the AS - Other variation B.I.c.3.a - Change in test procedure for the immediate packaging of the AS - Minor changes to an approved test procedure				
II/0066	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/06/2017		SmPC	Section 5.1 of the Summary of Product Characteristics (SmPC) for Champix has been revised and now includes a description of the results of Study A3051148.
II/0064	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/06/2017		SmPC, Labelling and PL	The product information for Champix was amended to include the addition of information regarding Study A3051078 (Varenicline Pregnancy Cohort Study), a prospective population-based cohort study comparing the occurrence of major congenital malformations among infants exposed and not exposed to varenicline in utero in mothers who smoked.

					Changes were made to Section 4.6 (Fertility, pregnancy and lactation) and Section 5.1 (Pharmacodynamic properties). In particular, to convey that it is preferable to avoid the use of Champix while pregnant, Section 4.6 now reads: "A moderate amount of data on pregnant women indicated no malformative or foetal/neonatal toxicity of varenicline. Animal studies have shown reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy."
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/07/2016		Labelling and PL	
R/0061	Renewal of the marketing authorisation.	28/04/2016	29/06/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Champix in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0062	The MAH submitted the final study report of study A3051123 and updated sections 4.4 and 5.1 of the SmPC to reflect the study results. Annex II, package leaflet and Risk Management Plan were also updated accordingly. In addition, the MAH took the opportunity to remove the Black Triangle and to introduce minor amendments to the labelling. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2016	29/06/2016	SmPC, Annex II, Labelling and PL	Varenicline was evaluated in a randomised, double-blind, active and placebo-controlled study that included subjects with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). The conducted Study A3051123 showed that varenicline had efficacy both in smokers with or without a prior history of psychiatric disorder. The adverse events profile of varenicline in A3051123 corresponded with the varenicline known safety profile. Varenicline was not associated with a greater risk of suicide-related events, or with a greater risk of other clinically significant neuropsychiatric events, compared to placebo or to bupropion or nicotine replacement therapy.

					This was the case in smokers with or without a prior history of psychiatric disorder.
IA/0060	A.7 - Administrative change - Deletion of manufacturing sites	03/12/2015	n/a		
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2015	17/05/2016	Labelling and PL	
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	17/05/2016	PL	
II/0057	Update of sections 4.4 and 5.1 of the SmPC in order to include information on Neuropsychiatric Safety (NPS) analyses of clinical studies and from observational studies. The MAH took the opportunity to implement minor editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	17/05/2016	SmPC	Analyses of clinical trial data did not show evidence of an increased risk of serious neuropsychiatric events with varenicline compared to placebo. In addition, independent observational studies have not supported an increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients prescribed nicotine replacement therapy (NRT) or bupropion.
II/0056	Update of section 4.5 of the SmPC in order to include further information on alcohol interaction after analysis of post marketing data. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	17/05/2016	SmPC and PL	There have been post marketing reports of increased intoxicating effects of alcohol in patients treated with varenicline. A causal relationship between these events and varenicline use has not been established.

PSUV/0054	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
II/0053	Update of sections 4.2 and 5.1 of the SmPC based on data from Study A3051075, a Phase 4, multi-national, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of varenicline compared to placebo for smoking cessation through reduction. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	11/02/2015	SmPC and PL	This variation application is based on data from Study A3051075, a double-blind, placebo-controlled study to evaluate the efficacy and safety of varenicline compared to placebo for smoking cessation through reduction, which enrolled smokers who were not able or willing to quit abruptly. Subjects gradually reduced the number of cigarettes smoked over a 12-week treatment period prior to quitting and to continue with another 12 weeks of treatment. The study demonstrated that a gradual quit approach, with a reduction in the number of cigarettes smoked prior to quitting has efficacy for smokers who will not or cannot quit smoking abruptly. New safety concerns for varenicline use would not be expected using this approach, and the study did not give rise to new safety concerns. The CHMP considered that Champix has a positive benefit/risk balance in smokers who will not/cannot quit smoking abruptly.
IAIN/0055	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	23/10/2014	11/02/2015	Annex II and PL	
II/0051	Update of Annex II based on submission of the final Report on Overall Evaluation of Psychiatric Events from pooled data from five clinical studies (A30151072, A3051115, A3051095, A3051122 and A3051139). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	25/09/2014	11/02/2015	Annex II	As requested by the CHMP, the MAH has conducted meta-analyses, pooling data regarding risk of suicide and/or psychiatric symptoms from 5 randomized, placebo controlled studies of varenicline, rating study subjects with the Columbia Suicide Severity Rating Scale, as well as data reported from the total of 18 randomized, placebo controlled varenicline studies. These analyses do not show statistically significant

	authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				differences between varenicline and placebo in the incidence rates of suicidal ideation or behaviour, in the incidence rate of hostility/aggression, or in the incidence rates of various psychiatric symptoms/disorders with the exception of sleep related symptoms. There were no clinical results reported from the studies that give rise to concern. The results from study A3051122, a study of stable patients with depressive disorder where special emphasis was placed on retrieving information about the incidence of hostility/aggression, suggest that hostility and increased aggression is perhaps more common in subjects treated for smoking tobacco/nicotine dependence than has previously been reported. In study A3051122 the incidence of these symptoms was higher in the varenicline-treated group, but it is plausible that this may in part be a result of varenicline-treated subjects reducing their tobacco/nicotine consumption. Moreover, as stated above, the overall meta-analysis of hostility/aggression does not show an increased risk associated with varenicline compared with placebo. The MAH's obligation to conduct the post-authorisation measure was fulfilled, without new concerns about suicidality or psychiatric events arising. The results do not change the positive benefit-risk balance of varenicline. The corresponding obligation was deleted from Annex II.
IA/0052	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	25/04/2014	n/a		

II/0049	Update of section 4.8 of the SmPC in order to update the safety information, including a re-assessment of the Adverse Reactions profile based on pooled data from 18 placebo-controlled pre- and post-marketing studies with varenicline. The Package Leaflet (section 4) was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	11/02/2015	SmPC and PL	To account for the completion of new clinical studies since approval of Champix in 2006, the MAH conducted an exercise to determine if the profile of Adverse Drug Reactions (ADRs) listed in the Product Information (SmPC and PL) remained accurate. To this end, pooled safety data from 18 placebo-controlled studies including over 5000 patients treated with varenicline were analysed based on the all-causality adverse events set. As a result, 13 side effects had their frequency categorization upgraded and 34 side effects had their frequency categorization downgraded. In addition, 12 new side effects were added to the product information, namely: Conjunctivitis, Angina pectoris, Tachycardia, Hot flush, Upper respiratory tract inflammation, Rhinitis allergic, Toothache, Arthralgia, Myalgia, Back pain, Pollakiuria (frequent daytime urination) and Influenza like illness.
PSUV/0050	Periodic Safety Update	05/12/2013	n/a		Update of section 4.4 and 4.8 of the SmPC with regard to seizure related events. The update included a warning in section 4.4 regarding seizures in patients with or without a history of seizures, and addition of 'seizures' in section 4.8, under the class nervous system disorders, with a frequency of uncommon. This frequency was calculated from the clinical trials data set. The Package Leaflet was updated accordingly.
II/0047	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/11/2013	06/06/2014	SmPC	The effectiveness of re-treatment with varenicline has not previously been studied in full-scale clinical trials. Study A3051139 was designed to compare the efficacy and safety of re-treatment with varenicline with placebo in subjects who had previously taken varenicline and had been unable to stop smoking or who had relapsed.

					This study provided evidence that re-treatment with varenicline can benefit smokers who either failed to quit while taking varenicline or relapsed after taking it. Re-treatment with varenicline was generally well-tolerated, with a safety profile consistent with previous studies of varenicline-naïve subjects and did not reveal any new safety concerns. The following text was added to section 4.2 of the SmPC: "Patients who are motivated to quit and who did not succeed in stopping smoking during prior Champix therapy, or who relapsed after treatment, may benefit from another quit attempt with Champix".
IB/0048/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	14/11/2013	06/06/2014	SmPC	
IB/0046/G	This was an application for a group of variations. B.II.d.z - Change in control of the Finished Product - Other variation B.II.d.z - Change in control of the Finished Product - Other variation	04/09/2013	n/a		

II/0045	Revision of Section 4.4 Special warnings and precautions for use and Section 5.1 Pharmacodynamic properties of the SmPC to reflect data from a completed clinical study (A3051122) to measure the Safety and Efficacy of Champix for Smoking Cessation in people with depression. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	27/06/2013	06/06/2014	SmPC, Annex II, Labelling and PL	The results of the Study A3051122 showed that varenicline is effective for smoking cessation in patients with major depressive disorder on stable antidepressant treatment and/or who had a major depressive episode in the previous 2 years and were successfully treated. With regards to Safety, the analyses of the psychiatric measurement did not reveal differences between varenicline and placebo and showed no overall worsening of depression in either treatment group. Section 4.4 was updated to reflect the data, and the study results are now presented in Section 5.1.
II/0043/G	This was an application for a group of variations. To add a new specification for a specified impurity. To add a new alternative blister packaging material (PVC/alu) To add new presentations within the range of the currently approved pack sizes with the new alternative blister packaging material (PVC/alu). B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets,	21/02/2013	06/06/2014	SmPC and Labelling	

	ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				

	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
II/0041	Update of sections 4.4 and 5.1 of the SmPC to update the safety information with data emerging from a meta-analysis of Cardiovascular events. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	19/11/2012	SmPC and PL	This type II variation updated the Summary of Product Characteristics (SmPC) following completion of a pooled analysis of cardiovascular (heart or blood vessel) side effects in controlled varenicline clinical studies. The CHMP supported that the analysis should be mentioned in the SmPC, with a description including its main results and mentioning the fact that the increase in risk observed with Champix was higher in patients with higher cardiovascular risk than in patients with lower cardiovascular risk. The SmPC now details the results of the analysis. The CHMP considered that the data assessed on the cardiovascular effects do not change the benefit-risk balance for Champix in smoking cessation in adults and that the revised wording of the product information adequately reflects the main findings of the CV meta-analysis. Section 2 of the Package Leaflet: Information for the User, Take care with CHAMPIX, was amended to reflect changes made to section 4.4 and section 5.1 of the SmPC, and now reads: Cardiovascular symptoms

					New or worse heart or blood vessel (cardiovascular) problems have been reported primarily in people who already have cardiovascular problems. Tell your doctor if you have any changes in symptoms during treatment with CHAMPIX. Get emergency medical help right away if you have symptoms of a heart attack or stroke.
IG/0169/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	08/06/2012	n/a		
II/0039	Following CHMP review of the Risk Management Plan version 6.0 for Champix, it was requested that the results from study A3051070 be provided once completed. With this variation, Section 5.2 (Pharmacokinetics) of the SmPC was updated with the results from this study. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/03/2012	13/04/2012	SmPC and Annex II	The primary objective of study A3051070 was to characterise the multiple-dose pharmacokinetics of varenicline in adolescent male and female smoking subjects. The information provided in Section 5.2 (Pharmacokinetics) of the SmPC was updated, and now includes the results of both the single-dose and multiple-dose PK studies. However, since efficacy was not an objective of study A3051070 (which was too small for any statistic evaluation of efficacy), the CHMP recommended reiterating the message already given in section 4.2 of the SmPC that efficacy and safety has not been demonstrated in the paediatric population below 18 years of age, and no recommendation on a posology can be made.

IB/0040/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	04/04/2012	n/a		
II/0038	Update of section 4.8 of the SmPC to include reference to 'diabetes', 'hyperglycaemia' and 'somnambulism' further to requests from CHMP following review of PSUR 8. The Package Leaflet updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/02/2012	21/03/2012	SmPC and PL	Following requests from the CHMP resulting from review of PSUR 8, reference to the side effects "diabetes", "hyperglycaemia" and "somnambulism" was included in the table of side effects in section 4.8 of the SPC with a frequency "Not known". The PL was updated accordingly, and now lists "diabetes", "high blood sugar" and "sleep walking" in its section 4 (Possible side-effects).
II/0036	Update of sections 4.4 (Special warnings and precautions for use) and 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics (SPC) in order to update the safety information and include a mention of the fact that limited data are	15/12/2011	20/01/2012	SmPC	The CHMP had requested a Safety study to evaluate the risk of Champix treatment in schizophrenic patients as a Follow up measure. Following this request, the MAH conducted a safety study of Champix (varenicline) for smoking cessation in patients with

	available from a single smoking cessation study (A3051072) in patients with stable schizophrenia or schizoaffective disorder. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				psychosis (Study A3051072). After finalization of Study A3051072, its results were evaluated as part of FUM 008.2. This assessment led to a request for clarification to the MAH, who, within their variation application for this procedure (II/36), provided answers to the points raised by the CHMP and at the same time submitted wording to update the SPC for Champix in accordance to the findings emerging from Study A3051072. The key messages added to the SPC were that “Limited data are available from a single smoking cessation study in patients with stable schizophrenia or schizoaffective disorder” and that “The limited data available from this single smoking cessation study are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.”
II/0034	The Product Information for Champix was revised (Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects, Section 5.1 Pharmacodynamic properties of the Summary of Product Characteristics (SPC) and Section 2 (Before you take Champix) and 4 of the Package Leaflet) with information regarding cardiovascular and cerebrovascular events. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	21/11/2011	SmPC and PL	In July 2011, the results of a large pooled data study (meta-analysis) of Champix’s side effects affecting the heart and blood vessels were published in the literature. The study, published in the Canadian Medical Association Journal on Monday 4 July, looked at the number of cardiovascular events seen in a total of 8,216 people taking either Champix or placebo in 14 randomised clinical trials lasting up to a year. The events included heart attack, stroke, disruption of the heart rhythm, heart failure and death related to cardiovascular problems. The largest of the studies included over 700 patients with pre-existing cardiovascular disease. The meta-analysis found that events were rare in both groups, but that there was a slightly increased number in the people taking Champix: 1.06% of those taking Champix had an event (52 out of 4,908) compared with 0.82% of those

					taking placebo (27 out of 3,308). This did not result in a difference in death rates between the two groups. The Committee identified a number of limitations of the meta-analysis, including the low number of events seen, the types of events counted, the higher drop-out rates in people receiving placebo, the lack of information on the timing of events, and the exclusion of studies in which no-one had an event. Because of these limitations, the Committee could not draw robust conclusions from the meta-analysis. However, as recommended by the CHMP, Pfizer, the marketing-authorisation holder for Champix, included more information on cardiovascular events in the medicine's product information, as follows: - Appropriate warnings on risk of cardiovascular events were introduced in section 4.4 (Special warnings and precautions for use). - In Section 4.8 (Undesirable effects) of the SmPC cardiovascular events were previously presented in three different subsections. In order to improve clarity, the events "blood pressure increased, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, heart rate increased" were moved to the appropriate subsections. Furthermore, "stroke" was included in the section. - The description in the SmPC (section 5.1) on the study in over 700 subjects with cardiovascular disease has been made more informative in terms of cardiovascular safety. The text has been made more factual by including information on how many subjects experienced cardiovascular events in general and specific events such as myocardial infarction in each treatment group.

IA/0035	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	10/10/2011	n/a		
II/0033	The purpose of this type II variation was to update Section 4.8 (Undesirable effects) of the Summary of Product Characteristics (SPC) and Section 4 of the Package Leaflet (PL) with frequencies of adverse events reported in study A3051084 a Modified Prescription Event Monitoring (M-PEM) study in response to a request by CHMP made in November 2010 (FU2 034.2). C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/05/2011	17/06/2011	SmPC and PL	The Adverse Drug Reactions table in Section 4.8 of the SPC was updated to include the ADRs 'depression', 'anxiety' and 'hallucinations' with the frequency "Uncommon". A footnote was added at the bottom of the table to underline that the frequency "Uncommon" for depression, anxiety and hallucinations had been calculated using a different methodology from the frequencies of the rest of the Adverse Drug Reactions. Section 4 of the Package Leaflet was updated to reflect the SPC.
R/0032	Renewal of the marketing authorisation.	17/03/2011	07/06/2011	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considered that the benefit-risk balance of Champix remains positive, but considers that its safety profile is to be closely monitored for the following reasons: A number of safety issues have been identified for Champix, in particular neuropsychiatric changes (most notably depression, suicide-related events and aggressive behaviour) but also cardiovascular events. Given the serious nature of the above issues, their impact on the benefit-risk balance needs to be continuously evaluated. Thus, the CHMP decided that the MAH should continue to submit yearly

					PSURs until otherwise stated. Therefore, based upon the safety profile of Champix, which requires submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years' time.
IG/0044/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	02/03/2011	n/a	Annex II	
II/0030	Update of Sections 4.2 and 5.1 of the SPC and section 3 of the PL further to data emerging from clinical study A3051095. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	18/11/2010	20/12/2010	SmPC, Annex II and PL	The originally approved prescribing instructions of Champix recommended that the patient should determine a date to stop smoking, and dosing should begin one or two weeks before this date. In clinical study A3051095, the efficacy and safety of Champix was evaluated in smokers who had the flexibility of quitting between weeks 1 and 5 of treatment. The results of the study suggested that the flexible target quit date between week 2-5 may be an alternative option for those patients who are not willing or able to quit early in the

					treatment. Accordingly, the product information for Champix has been updated to reflect the concept that before starting a course of Champix, patients should usually decide on a date in the second week of treatment (between day 8 and day 14) when to stop smoking. If a patient is not willing or able to set a target quit date within 2 weeks, they may choose their own quit date within 5 weeks after starting treatment.
II/0029	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	23/09/2010	25/10/2010	SmPC	The studies presented in the initial Marketing Authorisation Application for Champix included only 'healthy' smokers. The MAH has conducted a post-marketing study in a population with mild to moderate chronic obstructive pulmonary disease (COPD), as this subpopulation has a pronounced need for smoking cessation. The study showed that varenicline is as efficacious and well-tolerated in the treatment of patients with COPD than among healthy smokers. Therefore, the MAH was requested to update the Product Information for Champix as, since smoking cessation is especially relevant in this population, it may be helpful for clinicians to be aware that varenicline could be used in patients with mild-moderate COPD. The following text has been added to section 5.1 of the SPC for Champix: "The efficacy and safety of CHAMPIX (1 mg twice daily) for smoking cessation in subjects with mild-moderate COPD was demonstrated in a randomised double-blind placebo-controlled clinical trial. In this 52-week duration study, patients received treatment for 12 weeks, followed by a 40-week non-treatment follow-up phase. The primary endpoint of the study was the CO-confirmed; 4-week Continuous Quit Rate (4W CQR) from

					week 9 through week 12 and a key secondary endpoint was the Continuous Abstinence (CA) from Week 9 through Week 52. The safety profile of varenicline was comparable to what was reported in other trials in the general population, including pulmonary safety."
IA/0031	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/09/2010	n/a		
II/0026	Update of section 5.1 (Pharmacodynamic properties) of the SPC with information emerging from a clinical study in patients with stable cardiovascular disease. Update of Summary of Product Characteristics	22/10/2009	03/12/2009	SmPC	The MAH submitted the results of an efficacy/safety study of varenicline in smokers with cardiovascular disease. It was agreed that the information on cardiovascular adverse events in this patient population is of relevance to the prescribers. New text was added to section 5.1, to convey the message that the efficacy and safety of varenicline was evaluated in cardiovascular compromised smokers. Efficacy and safety was similar to that observed in studies with non-cardiovascular compromised smokers.
II/0028	Update of sections 4.4 and 4.8 of the SPC in order to include reference to post-marketing reports of angioedema; severe cutaneous reactions (including Stevens-Johnson Syndrome and Erytema Multiforme) and additional neuropsychiatric events in patients using varenicline. Sections 2 and 4 of the PL have been changed accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	30/11/2009	Annex II and PL	Based on comments from the CHMP assessment of PSUR 3 for Champix, a cumulative review of angioedema-related events was performed by the MAH and submitted with PSUR 4. More recently, the MAH's post-marketing database was reviewed again for term Angioedema. As a result, reference to hypersensitivity reactions, including angioedema has been added to the Product Information. Additionally, the post-marketing database was searched for cases reporting severe skin reactions using the term 'Severe Cutaneous Adverse Reactions'. As a result, reference to rare

					but sever cutaneous reactions has been added to the Product Information. Instructions have been added to the PL to inform patients that they should stop taking Champix and contact their doctor immediately if they develop swelling of the face, mouth or throat, or if their skin starts to peel or blister. A review of all serious events in the Psychiatric Disorders was also performed to ensure that the Product Information appropriately characterises the types of neuropsychiatric events associated with varenicline treatment. This analysis led to inclusion of the following neuropsychiatric event categories in the Product Information: changes in thinking, anxiety, psychosis, mood swings, and aggressive behaviour.
II/0027	Changes to the quality control of the finished product. Update of or change(s) to the pharmaceutical documentation	22/10/2009	05/11/2009		
II/0023	Update of DDPS (Pharmacovigilance) Update of DDPS (Pharmacovigilance)	25/06/2009	27/08/2009	Annex II	The Detailed Description of the Pharmacovigilance System (DDPS) has been updated (version 2.0) in order to reflect various organisational changes as well as the change of the global safety database. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
II/0022	Update the the Package Leaflet (PL) for Champix with information concerning suicide related events (SRE) and neuropsychiatric risk, together with guidance for patients in section 2 "Take special care with Champix" of the PL, as recommended by the CHMP in January	25/06/2009	27/08/2009	PL	The Package Leaflet has been updated to clearly reflect, in patient-compatible language, the relevant SPC information concerning SRE and neuropsychiatric risk, together with guidance for patients in the "Take special care with CHAMPIX" section of the leaflet.

	2009. Update of Package Leaflet				The following new text has been introduced to section 2 of the PL: "There have been reports of depression, suicidal ideation and behaviour and suicide attempts in patients taking CHAMPIX. If you are taking CHAMPIX and develop agitation, depressed mood, changes in behaviour that are of concern to you, your family or doctor or if you develop suicidal thoughts or behaviours you should stop your treatment and contact your doctor immediately." Additionally, in section 4 of the PL, the following sentence has been given prominence by being moved from the end of the section to its beginning: "If you are taking CHAMPIX and develop agitation, depressed mood, changes in behaviour or suicidal thoughts you should stop your treatment and contact your doctor immediately."
IB/0025	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	04/08/2009	04/08/2009	SmPC, Labelling and PL	
II/0024	Update of the SPC and PL according to the outcome of the assessment of the fifth PSUR Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	03/08/2009	SmPC and PL	The fifth PSUR for Champix (covering the period of 10 May 2008 - 9 November 2008), contained a Cumulative Review of episodes of Aggression/Irrational Behaviour. Cases of aggression/Irrational behaviour have been reported, especially in patients with a psychiatric history. Therefore, a request was made by the CHMP for the terms aggression/irrational behaviour to be added the SPC and Package Leaflet. With this variation the terms were introduced to the Product Information, as requested.

II/0021	Update of section 4.8 of the Summary of Product Characteristics (SPC) to include information on "hallucinations" following the CHMP conclusions adopted in November 2008. Additionally, the contact phone numbers for the Irish, Slovenian and UK local representatives have been updated in the Package Leaflet (PL). Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	07/04/2009	SmPC and PL	The CHMP reviewed the data provided by the MAH on the issue of hallucinations observed during treatment with Champix. The CHMP concluded that, as there is at least a reasonable possibility of an association between its occurrence and use of Champix, 'hallucinations' needed to be included in the SPC, although a full causality could not be established for the cases seen. Consequently, the term has been included in section 4.8 of the SPC and section 4 of the PL by means of this variation procedure.
IA/0020	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	16/12/2008	n/a		
II/0019	Amendment of section 4.8 of the Summary of Product Characteristics (SPC) and section 4 of the Package Leaflet (PL) to include 'hypersensitivity reactions' (angioedema) further to publication of data in the scientific literature and recommendations from the CHMP following assessment of PSUR 3 and 4. Additionally, the Detailed Description of the Pharmacovigilance System (DDPS) in Module 1.8.1 of the Champix Marketing Authorisation has been updated, in accordance with the current pharmacovigilance guideline. Finally, the telephone numbers for the local representatives of the Marketing Authorisation Holder in Germany and Ireland in section 6 of the PL have been amended.	23/10/2008	25/11/2008	SmPC, Annex II and PL	A report by Thomas J. Moore et al, entitled 'Strong Safety Signals seen for new Varenicline Risks', by the U.S. Institute for Safe Medication Practices (ISMP) with regard to varenicline and new suspected risks was published (May 2008) by the US Institute for Safe Medication (ISMP). This article raised safety concerns in relation to varenicline and its possible association with adverse events such as, amongst others, skin reactions. Further to this, and based on recommendations from the CHMP further to assessment of PSUR 3 and 4 for Champix, the following text has been included to Section 4.8 (Undesirable Effects) of the Champix SPC: "There have also been reports of hypersensitivity reactions, such as angioedema and facial swelling." To reflect the above change, the following text (between inverted commas) has been added to section 4 of the PL: There have been reports of heart attack, depression, suicidal

	Update of Summary of Product Characteristics and Package Leaflet				thoughts “and hypersensitivity reactions (such as swollen face or tongue)” in patients attempting to quit smoking with Champix.
II/0016	Amendment of section 4.4 of the Summary of Product Characteristics and section 4 of the Package Leaflet to strengthen the wording regarding suicide-related events (SRE), and to include instructions on stopping Champix under certain circumstances. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	08/08/2008	SmPC and PL	In the context of a wider discussion on Champix that took place at the May 2008 PhVWP and CHMP meetings, a review of spontaneous reporting data on Suicide-Related Events (SRE) was presented and discussed. As a result of the discussion on SRE, the CHMP considered that updates to section 4.4 of the SPC and section 4 of the PL were required to strengthen the existing warnings with regards to SRE. In particular, mention of the fact that not all patients experiencing depression and suicidal thoughts had a previous history of psychiatric illness or had stopped smoking was added to the SPC. Moreover, instructions on stopping Champix and contacting doctors when patients develop agitation, depressed mood, changes in behaviour or suicidal thoughts were added to the Product Information.
IB/0018	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	01/08/2008	n/a		
IA/0017	IA_32_a_Change in batch size of the finished product - up to 10-fold	15/07/2008	n/a		
IB/0015	IB_33_Minor change in the manufacture of the finished product	13/05/2008	n/a		
IA/0013	IA_05_Change in the name and/or address of a manufacturer of the finished product	08/04/2008	n/a	Annex II and PL	

IB/0012	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	19/03/2008	19/03/2008	SmPC, Labelling and PL	
II/0011	Update of sections 4.4 and 4.8 of the Summary of Products Characteristics (SPC) to include information on depression, suicidal ideation and suicidal attempt. The Package Leaflet (PL) is being updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	28/02/2008	SmPC and PL	Further to the submission of the second Periodic Safety Assessment Report (PSUR) and additional data provided by the MAH, the CHMP reviewed reported cases of suicidal ideation (thinking about committing suicide) or attempted suicide in patients taking Champix. From the available data, and considering that stopping smoking itself can make people depressed, the CHMP could not definitely conclude on the actual association of the reported cases with Champix. However, the CHMP agreed that the Product Information should be updated to include information in this regard. The following warning was included in section 4.4 (Warnings and Precautions) of the SPC: "Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported while attempting to quit smoking with Champix. Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly." Section 4.8 (Side Effects) of the SPC was also updated to include that "Post-marketing cases of depression and suicidal ideation have been reported in patients taking varenicline". The PL was updated accordingly.

II/0010	Update of section 2 of the Package Leaflet (PL) to include a statement regarding possible exacerbation of psychiatric conditions in connection to smoking cessation, as requested by the CHMP in September 2007. Additionally, a sentence with clarifications regarding smoking after the quit date was added to section 1 of the PL. Finally, contact details of local representatives were also updated. Update of Package Leaflet	24/01/2008	28/02/2008	PL	Section 2 ("Before you take Champix") of the PL has been amended to include information on possible exacerbation of psychiatric conditions in connection to smoking cessation, as previously requested by the CHMP. In addition to this requested change, the MAH included further changes to the leaflet in their application. Specifically, a sentence with clarifications regarding smoking after the 'quit date' was added to section 1 ("What is Champix and what it is used for"). Finally, administrative changes to the details of the local representatives section were implemented.
IB/0008	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	15/11/2007	n/a		
IB/0007	IB_38_c_Change in test procedure of finished product - other changes	01/10/2007	n/a		
II/0006	Update of Section 4.8 (Undesirable Effects) of the SPC to include a statement indicating that post-marketing cases of myocardial infarction had been observed in patients taking varenicline. Update of Summary of Product Characteristics	22/03/2007	26/04/2007	SmPC	Following post-marketing reports of myocardial infarction in patients taking varenicline, the CHMP requested the SPC to be updated with this information. The MAH reviewed the post-marketing database and analysed all cases of myocardial infarction related events. From the analysis of the reported cases it can be concluded that the frequency of reported cases does not exceed what could be expected based on current epidemiological knowledge and most cases had coexisting cardiovascular risk factors. However, the presence of cardiovascular risk factors does not exclude an additional contributory risk from the use of varenicline. Therefore, the following information was added to section 4.8 of the SPC: "Post-marketing cases of myocardial infarction have been reported in patients taking varenicline.".

IB/0005	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	21/03/2007	21/03/2007	SmPC, Labelling and PL	
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/02/2007	n/a	PL	
IB/0004	IB_10_Minor change in the manufacturing process of the active substance	30/01/2007	n/a		
IB/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	18/12/2006	n/a	SmPC	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/12/2006	n/a	PL	