

## Procedural steps taken and scientific information after the authorisation

### Champix

#### MAJOR CHANGES<sup>1</sup>

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected <sup>2</sup>	Summary
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.	22/10/2009	03/12/2009	SPC	<p>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.</p> <p>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.</p>
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.	24/09/2009	30/11/2009	Annex II, PL	<p>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.</p> <p>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 severe cutaneous reactions has been added to the Product Information.</p> <p>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.</p>

<sup>1</sup> Major changes e.g. Type II variations, Annex II applications, Renewals and Annual Reassessments

<sup>2</sup> SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet)

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					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	Update of or change(s) to the pharmaceutical documentation  Changes to the quality control of the finished product.	22/10/2009	05/11/2009		
II/0023	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 2009.	25/06/2009	27/08/2009	PL	<p>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.</p> <p>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."</p> <p>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</p>

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					stop your treatment and contact your doctor immediately."
II/0024	Update of the SPC and PL according to the outcome of the assessment of the fifth PSUR	25/06/2009	03/08/2009	SPC, 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).	19/02/2009	07/04/2009	SPC, 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.
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	23/10/2008	25/11/2008	SPC, Annex II, 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 thoughts "and hypersensitivity reactions (such as swollen face or tongue)" in patients attempting to quit smoking with Champix.

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	Authorisation Holder in Germany and Ireland in section 6 of the PL have been amended.				
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.	26/06/2008	08/08/2008	SPC, PL	<p>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.</p> <p>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.</p>
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.	24/01/2008	28/02/2008	SPC, PL	<p>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.</p> <p>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</p>

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					<p>patients accordingly."</p> <p>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".</p> <p>The PL was updated accordingly.</p>
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.	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.
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.	22/03/2007	26/04/2007	SPC	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."

**MINOR CHANGES<sup>3</sup>**

No	Scope	Product Information affected <sup>2</sup>	Date <sup>4</sup>
IB/0025	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	SPC, Labelling, PL	04/08/2009
IA/0020	38_a_Change in test procedure of finished product - minor change to approved test procedure		16/12/2008
IB/0018	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release		01/08/2008
IA/0017	32_a_Change in batch size of the finished product - up to 10-fold		15/07/2008
IB/0015	33_Minor change in the manufacture of the finished product		13/05/2008
IA/0013	05_Change in the name and/or address of a manufacturer of the finished product	Annex II, PL	08/04/2008
IB/0012	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	SPC, Labelling, PL	19/03/2008
IB/0008	13_b_Change in test proc. for active substance - other changes (replacement/addition)		15/11/2007
IB/0007	38_c_Change in test procedure of finished product - other changes		01/10/2007
IB/0005	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	SPC, Labelling, PL	21/03/2007
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	06/02/2007
IB/0004	10_Minor change in the manufacturing process of the active substance		30/01/2007
IB/0002	42_a_01_Change in shelf-life of finished product - as packaged for sale	SPC	18/12/2006
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	14/12/2006

<sup>3</sup> Minor changes e.g. Type I variations and Notifications

<sup>4</sup> Date of entry into force of the change