# GLAXOSMITHKLINE CONSUMER HEALTHCARE v PFIZER

## Champix detail aid

**GlaxoSmithKline Consumer Healthcare complained about a Champix (varenicline) detail aid issued by Pfizer. GlaxoSmithKline marketed NiQuitin Clear Patch (nicotine), a nicotine replacement therapy (NRT). Both Champix and NiQuitin were indicated for smoking cessation.**

**The claims 'Champix at 12 weeks – significantly higher quit success vs NRT' and 'Champix at 12 weeks enables significantly more smokers to quit than NRT' appeared on page 6 of the detail aid. They were referenced to Aubin *et al* (2008) which was the first direct comparison of varenicline with a specific type of NRT.**

**GlaxoSmithKline was concerned that although Aubin *et al* showed significantly higher end of treatment (12 week) quit rates for Champix compared with NiQuitin, there was no significant difference in long term (52 week) quit rates between the two. This new evidence needed to be incorporated in any comparison of Champix and NRT to ensure that the promotional material was up-to-date and reflected all available evidence clearly.**

**GlaxoSmithKline did not dispute that the primary endpoint of the study showed a significantly greater quit success at the end of treatment with Champix than with NiQuitin Clear Patch. This difference was no longer significant at six and twelve months. However, the impression created was that Champix was more effective overall than NiQuitin Clear Patch which was not true.**

**GlaxoSmithKline considered that the longer term results must be given equal (if not greater) prominence to the short term results in an effort to balance the material.**

**The six and twelve month results were highly clinically relevant, with long term quit being the goal of all smoking cessation interventions. The fact that the short term results were the primary endpoint of Aubin *et al* did not negate this, and were likely to have been chosen simply for regulatory expediency. The real health benefits of smoking cessation required continued long term cessation. The European Medicines Evaluation Agency's (EMEA's) draft guidelines on smoking cessation products were clear that it should be persistent abstinence rates one year post treatment that were the primary endpoint, with end of treatment abstinence rates a secondary endpoint. The Cochrane collaboration, the National Institute for Health and Clinical Excellence (NICE) and the Thorax smoking cessation guidelines for health professionals all used trials with a minimum of six months' follow up on which to base their recommendations, and thus would only use the 6 and 12 month results from Aubin *et al*; Pfizer had defended the use of 12 week quit rates by stating that the NHS used 4 week quit rates as a target so 12 weeks was substantially longer than this. The NHS recognised the limitations of the reliance on 4 week quit rates, and ideally would use longer term outcomes. However, the surrogate marker of 4 week quit rates was used as a compromise (Ferguson *et al*, 2005).**

**The overall impression created was that Champix was more effective than NiQuitin Clear Patch, which although true for the short term end of treatment result, was not true for the more clinically relevant longer term results. GlaxoSmithKline alleged that the claims were misleading.**

**The detailed response from Pfizer is given below.**

**The Panel considered that it was clear that the data comparing quit success for Champix (55.9%) and NRT (43.2%) ($p<0.001$) was at 12 weeks (the primary endpoint of the study). The data for one year was included as the final bullet point and it was clear that the difference in quit success between Champix (26.1%) and NiQuitin (20.3%) was not statistically significant ($p=0.056$). The Panel did not accept that the data from Aubin *et al* had been presented in a misleading manner. The 12 week and 52 week data had been accurately reported and the statistical significance of the results stated. It was clear that the numerical difference in favour of Champix at 52 weeks was not statistically significant. Both the 12 week and the one year data would be of interest to prescribers. No breach of the Code was ruled.**

**Page 7 was headed 'Champix – numbers needed to treat in smoking cessation'. Beneath which data from the Cochrane Review was presented. The NNT to achieve each additional successful quitter compared with placebo was 20 for all types of NRT, 15 for bupropion and 8 for Champix,**

**GlaxoSmithKline alleged that the discussion on page 7 of the NNT in smoking cessation was misleading as it was not an up-to-date evaluation of all the evidence since the publication of Aubin *et al* of Champix vs NiQuitin Clear Patch; the NNTs had been calculated by others on the basis of these results. There were shortcomings to the use of the Cochrane review as all types of NRT were pooled in this comparison, when it was clear there were differences between the different dosage forms and combinations (patch, gum, lozenge, nasal spray, combination), doses, support methods, analyses, patient groups and health professional intervention**

**(eg over the counter NRT use without the intervention of a health professional vs GP-led prescribing).**

**On the basis of Aubin *et al*, it had been calculated that to get one extra quitter over and above that gained by using NiQuitin Clear Patch, the NNT was 18 extra Champix patients giving an incremental cost of £1,155 per patient. This was clearly at odds with the claim which did not present an up-to-date evaluation of all the evidence.**

**The Panel noted that page 7 reported the NNT to achieve each additional successful quitter with, *inter alia*, all types of NRT (20) and Champix (8) vs placebo. Updated NNT data vs placebo had been published by Cochrane on 16 July 2008. The complaint from GlaxoSmithKline was received on 15 July 2008.**

**The Panel noted Pfizer's submission that the Champix NNT data that could be derived from Aubin *et al* would be compared with NiQuitin Clear Patch and not placebo.**

**The Panel considered that at the time the complaint was made the NNT data compared to placebo was up-to-date. The publication of the updated Cochrane data on 16 July meant that from that date the data in the detail aid was not up-to-date. However this was after the complaint was made. Thus the Panel ruled no breach of the Code. The Panel did not consider that the NNT data vs placebo had to be updated following publication of Aubin *et al* and thus no breach was ruled.**

**The claim 'Added benefit of cost-effectiveness' appeared on page 7 of the detail aid as a subheading followed by the claim 'Champix was more cost-effective than NRT patches or bupropion (using indirect and direct comparisons respectively)' which was referenced to O'Regan *et al* (2007).**

**GlaxoSmithKline alleged that the claim was misleading as it did not reflect up-to-date evidence fairly. Aubin *et al* showed no significant difference in long term quit rates and should be used in any cost-effectiveness models rather than older, indirect comparisons which also had the limitations outlined above.**

**The Panel noted that O'Regan *et al* was a brief abstract which had calculated cost effectiveness data for Champix, NRT patch and bupropion based on quit rates at 1 year of 22.5%, 15.5% and 15.7% respectively.**

**The Panel had little information about the methods used but assumed that the data from Aubin *et al* could be fed into it. It was true that Aubin *et al* was not a cost effectiveness study but it had provided data on quit rates that might be relevant to the cost-effectiveness claim. The Panel noted, however, that although Aubin *et al* post-dated O'Regan *et al*, there was no data to show that even if the later results had been added to the model used by O'Regan *et al* they would have changed the overall, broad conclusion that Champix was more cost-effective than NRT patches or bupropion. On the basis of the data before it the Panel ruled no breach of the Code.**

**GlaxoSmithKline alleged that patient safety was paramount and the safety and tolerability page falsely reassured prescribers about the lack of serious events associated with Champix. It referred to the claim 'Favourable safety profile in approximately 4,000 treated smokers'. A similar claim appeared on the key messages summary page. Using this type of wording did not give the reader a true picture of the safety issues. Page 11 did not make clear that there had been a number of reports of myocardial infarction (MI) as itemised in the Champix summary of product characteristics (SPC), and neither was this listed in the prescribing information.**

**Whether or not a causal relationship had been established or the reports were infrequent or most patients had underlying risk factors, the EMEA required a statement about MI to be added to the side-effects section of the SPC. The EMEA concluded that 'the presence of cardiovascular risk factors cannot exclude the possibility of an additional contributory risk from the use of varenicline'. As such, the risk of MI should be included in the prescribing information as this was a serious side-effect. The fact that the MHRA had accepted Pfizer's rationale for not including MI in the prescribing information did not mean that there was not a breach of the Code. The prescriber was not able to make an informed appraisal of the medicine.**

**The Panel noted that in July 2007 the statement 'Post marketing cases of myocardial infarction, depression and suicidal ideation have been reported in patients taking varenidine (see section 4.4)' had been added to the Champix SPC. The statement appeared beneath a table listing all adverse reactions which occurred at an incidence greater than placebo. Section 4.4 included additional information about depression and suicidal ideation but gave no additional information about MI. The prescribing information in the detail did not mention MI. A statement to see the SPC for less commonly reported side effects was included.**

**The Panel did not consider that in the circumstances the failure to include in the prescribing information the post marketing surveillance data in relation to MI meant that the prescribing information did not meet the requirements of the Code that a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and contra-indications, relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of products characteristics, together with a statement that prescribers should consult the summary of products characteristics in relation to other side-effects be included. No breach of the Code was ruled.**

**The Panel did not consider that the absence of information about MI on the page detailing the safety and tolerability of Champix, on the key messages page or in the prescribing information meant that the prescriber was not in a position to make an informed appraisal of the medicine. No breach of the Code was ruled.**

GlaxoSmithKline Consumer Healthcare complained about a Champix (varenicline) detail aid issued by Pfizer Limited. GlaxoSmithKline marketed NiQuitin Clear Patch (nicotine), a nicotine replacement therapy (NRT). Both Champix and NiQuitin were indicated for smoking cessation.

This case was considered under the 2008 Constitution and Procedure. The clauses cited, 4.2, 7.2, 7.3 and 7.9, were the same in the 2006 Code as the 2008 Code.

**1 Claims 'Champix at 12 weeks – significantly higher quit success vs NRT' and 'Champix at 12 weeks enables significantly more smokers to quit than NRT'**

The claims at issue appeared on page 6 of the detail aid. They were referenced to Aubin *et al* (2008) which was the first direct comparison of varenicline with a specific type of NRT.

## COMPLAINT

GlaxoSmithKline was concerned that although Aubin *et al* showed significantly higher end of treatment (12 week) quit rates for Champix compared with NiQuitin, there was no significant difference in long term (52 week) quit rates between the two. This new evidence needed to be incorporated in any comparison of Champix and NRT to ensure that the promotional material was up-to-date and reflected all available evidence clearly.

In this area of emerging scientific opinion, previous discussions on the relative efficacy of the two treatment types had been based on indirect comparisons where results for all different types of NRT had been pooled so that 'apples' were not compared to 'pears' but to 'fruit'. This newly published direct comparison gave a clearer picture of the relative efficacies of NiQuitin Clear Patch and Champix.

GlaxoSmithKline did not dispute that the primary endpoint of the study showed a significantly greater quit success at the end of treatment with Champix than with NiQuitin Clear Patch. This difference was no longer significant at six and twelve months.

However, the impression created was that Champix was more effective overall than NiQuitin Clear Patch which was not true. This impression was created by:

- the headline 'Champix at 12 weeks – significantly higher quit success rate vs NRT' which set the tone for the page,
- the emphasis of the bar chart that only described the end of treatment (12 week) results,
- the prominent '2x' in the claim 'approximately 2x greater odds of quitting smoking with Champix at 12 weeks vs NRT patch (odds ratio 1.70; p<0.001)',
- the strap line at the bottom of the page, 'Champix at 12 weeks enables significantly more smokers to quit than NRT',
- the inclusion of the unqualified claim 'Significantly higher quit success at 12 weeks vs NRT patch, bupropion or placebo' as a key message on the back page.

The Code required comparisons to be accurate, balanced, fair, objective and unambiguous and based on an up-to-date evaluation of all evidence and reflect that evidence clearly. They must not mislead directly or by implication, by distortion, exaggeration or undue emphasis. Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. This was particularly true for issues where clinical opinion was evolving. As such GlaxoSmithKline considered that the longer term results must be given equal (if not greater) prominence to the short term results in an effort to balance the material.

The six and twelve month results were highly clinically relevant, with long term quit being the goal of all smoking cessation interventions. The fact that the short term results were the primary endpoint of Aubin *et al* did not negate this, and were likely to have been chosen simply for regulatory expediency. The real health benefits of smoking cessation required continued long term cessation, and because of this, the European Medicines Evaluation Agency's (EMEA's) draft guidelines on smoking cessation products were clear that it should be persistent abstinence rates one year post treatment that were the primary endpoint, with end of treatment abstinence rates a secondary endpoint. The Cochrane collaboration, the National Institute for Health and Clinical Excellence (NICE) and the Thorax smoking cessation guidelines for health professionals all used trials with a minimum of six months' follow up on which to base their recommendations, and would only use the 6 and 12 month results from Aubin *et al* when they next updated; they would not use the end of treatment data-point, even if it was the primary endpoint as it was not as clinically relevant as the longer term results. Pfizer defended the use of 12 week quit rates by stating that the NHS used 4 week quit rates as a target so 12 weeks was substantially longer than this. However, the NHS did not have the capacity to follow patients long term, and 4 week quit rates were used as a measure of success of their overall intervention. They were not intended as a robust comparison between treatments, but a target set by the NHS for it to monitor progress within a locality on a rolling basis. The NHS recognised the limitations of the reliance on 4 week quit rates, and ideally would use longer term outcomes. However, because their collection could be expensive and time-consuming, detracting from the delivery of core services, it relied on the surrogate marker of 4 week

quit rates as a useful compromise (Ferguson *et al*, 2005).

The overall impression created was that Champix was more effective than NiQuitin Clear Patch, which although true for the short term end of treatment result, was not true for the more clinically relevant longer term results. The omission of any reference to the head-to-head long term quit rate results on the back page (key messages) clearly demonstrated Pfizer's intent to persuade prescribers that Champix was significantly more effective than the NRT patch when this was not so in the long term. It was vital that prescribers were given adequate and balanced information to enable them to form their own opinion about the value of medicines, particularly when new data such as this might challenge their current beliefs. GlaxoSmithKline alleged that the detail aid was misleading and in breach of Clause 7.2.

## RESPONSE

Pfizer explained that the primary objective of Aubin *et al* was to compare a 12 week standard regimen of Champix with a 10 week standard regimen of transdermal NRT, and it was the primary endpoint result that was the focus of this section of the detail aid. As detailed in Section 3.2.2.4 of the ICH General Considerations for Clinical Trials, a primary endpoint should reflect clinically relevant effects and was typically selected based on the principal objective of the study. Pfizer also included a longer term secondary endpoint, notably the 52 week data, despite its understanding that secondary endpoints were regarded as for further exploratory use only. Inclusion of the 52 week data in the detail aid facilitated more in-depth discussion with the health professional.

Pfizer submitted that it clearly stated that the difference between Champix and the NRT patch at 52 weeks was not significant and showed the p value. The study was powered for the primary endpoint and not at 52 weeks, giving a scientific rationale as to why Champix was numerically but not statistically superior at 52 weeks. Furthermore, in the pre-specified sensitivity analysis looking at the 'all randomised' population at 52 weeks, Champix was both numerically and statistically superior to the NiQuitin Clear patch [25.9% vs 19.8%, OR 1.44 (1.02–2.03), p=0.040].

Pfizer noted GlaxoSmithKline's concern that the 'impression' created by this section of the detail aid was that Champix was more effective overall than NiQuitin Clear patch.

Pfizer disagreed that its approach created a misleading impression. The page in the detail aid had a headline and strapline that represented the primary endpoint of the study presented, and it was explicitly clear that the treatment significance was at 12 weeks only (ie short term quit rate). Similarly, the bar chart demonstrated this primary endpoint in a balanced manner, which helped the representative discuss the data with a health professional. Furthermore it was reasonable to highlight the primary endpoint within the text as it was the principal aim of the study. Finally, the comment around the alleged unqualified claim 'Significantly higher quit success at 12 weeks vs NRT patch, bupropion or placebo' in the key messages page was invalid, since this was clearly referenced to clinical papers. It was not misleading as it clearly referred to the correct time span within the clinical studies. Pfizer therefore did not believe that the presentation of this information was in breach of Clause 7.2.

Pfizer also disagreed that the longer term results should be given equal (if not greater) prominence to the short-term results in an 'effort to balance the material'; the page represented a balanced overview of Aubin *et al*. The study was not powered for the longer term result, it was a secondary endpoint, evaluated for exploratory means only. It was consistently made explicitly clear that the significant difference in quit rates between Champix and NiQuitin Clear patch was seen in the primary endpoint, at end-of-treatment.

Pfizer noted that GlaxoSmithKline had included information from the draft 'Guideline on the development of medicinal products for the treatment of nicotine dependence' that was sent on 19 July 2007 by the EMEA for consultation. Pfizer would review the document in its entirety once it had been finalised, and incorporate this information into its thinking around future clinical trials with Champix.

Pfizer noted that GlaxoSmithKline also referred to the Cochrane collaboration using only 6 and 12 month results. This update was recently published online in 'Nicotine receptor partial agonists for smoking cessation' on 16 July 2008 (Issue 3, 2008). The authors included Aubin *et al* in their review and stated that 'One open-label trial of varenicline versus nicotine replacement therapy demonstrated a modest benefit of varenicline over NRT with a RR at week 52 of 1.31 (95%CI 1.01 to 1.71)'. The results within this Cochrane review were in keeping with the overall presentation of Aubin *et al* within the detail aid.

Pfizer disagreed that the overall impression in the detail aid of the head-to-head study of Champix vs NiQuitin Clear patch was misleading (Clause 7.2). Throughout the material the timeframe was clearly stated with the inclusion of the primary endpoint of the study and details of the 52 week secondary endpoint were provided to facilitate a more in-depth discussion with the health professional.

## PANEL RULING

The Panel examined page 6 of the detail aid. It was clear that the data comparing quit success for Champix (55.9%) and NRT (43.2%) (p<0.001) was at

12 weeks (the primary endpoint of the study). The data for one year was included as the final bullet point and it was clear that the difference in quit success between Champix (26.1%) and NiQuitin (20.3%) was not statistically significant (p=0.056). The Panel did not accept that the data from Aubin *et al* had been presented in a misleading manner. The 12 week and 52 week data had been accurately reported and the statistical significance of the results stated. It was clear that the numerical difference in favour of Champix at 52 weeks was not statistically significant. Both the 12 week and the one year data would be of interest to prescribers. No breach of Clause 7.2 was ruled.

**2 Number Needed to Treat (NTT)**

Page 7 was headed 'Champix – numbers needed to treat in smoking cessation'. Beneath which data from the Cochrane Review was presented. The NNT to achieve each additional successful quitter compared with placebo was 20 for all types of NRT, 15 for bupropion and 8 for Champix,

## COMPLAINT

GlaxoSmithKline alleged that the discussion on the this page of the NNT in smoking cessation was misleading as it was not an up-to-date evaluation of all the evidence since the publication of Aubin *et al* of Champix vs NiQuitin Clear Patch; the NNTs had been calculated by others on the basis of these results. There were shortcomings to the use of the Cochrane review as all types of NRT were pooled in this comparison, when it was clear there were differences between the different dosage forms and combinations (patch, gum, lozenge, nasal spray, combination), doses, support methods, analyses, patient groups and health professional intervention (eg over the counter NRT use without the intervention of a health professional vs GP-led prescribing).

However, leaving that aside, the publication of Aubin *et al* meant that there was more and relevant evidence that needed to feed in to any NNT calculation and this was not done in the detail aid.

On the basis of Aubin *et al*, it had been calculated that to get one extra quitter over and above that gained by using NiQuitin Clear Patch, the NNT was 18 extra Champix patients giving an incremental cost of £1,155 per patient. This was clearly at odds with the claim which did not present an up-to-date evaluation of all the evidence, in breach of Clauses 7.2 and 7.3.

## RESPONSE

Pfizer submitted that the NNT evidence was from the original Cochrane Review – 'Nicotine receptor partial agonists for smoking cessation', which was published online in January 2007 as part of the Cochrane Library. Since this information source provided high-quality, independent evidence Pfizer considered that it was an appropriate reference. The primary objective of this Cochrane Review was to assess the efficacy and tolerability of nicotine receptor partial agonists for smoking cessation. As part of this evaluation, the NNT to achieve each additional successful quitter was derived from the pooled difference between placebo and treatment quit rates. For comparison with Champix, the Cochrane Review estimated NNTs from recent meta-analyses of NRT and bupropion. The values reported were for 'all types of NRT', and Pfizer therefore could not include values for different dosage forms and combinations, different doses/support methods and so on, as this level of information was not available.

Pfizer noted that NNT data had not been published for Aubin *et al* and NNTs derived from this study would compare Champix with the NRT patch rather than placebo.

Since April 2008, when the Champix detail aid was printed, as described above the Cochrane Collaboration had updated the original 'Nicotine receptor partial agonists for smoking cessation' document, including updated NNT values (published 16 July 2008). The original values for NNT to achieve each additional successful quitter compared with placebo were: all types of NRT, 20; bupropion, 15 and Champix, 8. In the updated document, the values have been revised: all types of NRT 23, bupropion, 18 and Champix 10. Pfizer stated that it could use these updated NNT values in future materials, now that they had been published.

Pfizer did not agree that the presentation of the original NNT values from the Cochrane review was misleading and therefore denied breaches of Clauses 7.2 and 7.3.

## PANEL RULING

The Panel noted that page 7 reported the NNT to achieve each additional successful quitter with, *inter alia*, all types of NRT (20) and Champix (8) vs placebo. Updated NNT data vs placebo had been published by Cochrane on 16 July 2008. The complaint from GlaxoSmithKline was received on 15 July 2008.

The Panel noted Pfizer's submission that the Champix NNT data that could be derived from Aubin *et al* would be compared with NiQuitin Clear Patch and not placebo.

The Panel considered that at the time the complaint was made the NNT data compared to placebo was up-to-date. The publication of the updated Cochrane data on 16 July meant that from that date the data in the detail aid was not up-to-date. However this was after the complaint was made. Thus the Panel ruled no breach of Clauses 7.2 and 7.3. The Panel did not consider that the NNT data vs placebo had to be updated following publication of Aubin *et al*. Thus no breach of Clauses 7.2 and 7.3 was ruled.

**3 Claim 'Added benefit of cost-effectiveness'**

The claim appeared on page 7 of the detail aid as a subheading followed by the claim 'Champix was more cost-effective than NRT patches or bupropion (using indirect and direct comparisons respectively)' which was referenced to O'Regan *et al* (2007).

## COMPLAINT

GlaxoSmithKline alleged that the claim was misleading as it did not reflect up-to-date evidence fairly. As noted above, Aubin *et al* showed no significant difference in long term quit rates and should be used in any cost-effectiveness models rather than older, indirect comparisons which also had the limitations outlined above. O'Regan *et al* was out of date since the publication of the new head-to-head data in Aubin *et al*. GlaxoSmithKline alleged breaches of Clauses 7.2 and 7.3.

## RESPONSE

Pfizer stated that O'Regan *et al* was a relevant and up-to-date reference for the claim 'Champix was more cost-effective than NRT patches or bupropion (using indirect and direct comparisons respectively)'. GlaxoSmithKline had not provided a more up-to-date cost-effectiveness reference. The results of Aubin *et al* did not include a cost-effectiveness analysis. Thus Pfizer denied breaches of Clauses 7.2 and 7.3 as the claim was an up-to-date evaluation of the evidence.

## PANEL RULING

The Panel noted that O'Regan *et al* was a brief abstract which had calculated cost effectiveness data for Champix, NRT patch and bupropion based on quit rates at 1 year of 22.5%, 15.5% and 15.7% respectively. Efficacy was based on biochemically confirmed quit rates at one year taken from pooling the results of published clinical trials.

The data had been produced by a Pfizer team using a model which calculated the cost and benefits that would accrue from smoking cessations over a 20 year period. The model calculated savings in direct healthcare costs in Scotland.

The Panel had little information about the methods used in the cost effectiveness model but assumed that the data from Aubin *et al* could be fed into it. It was true that Aubin *et al* was not a cost effectiveness study but it had provided data on quit rates that might be relevant to the cost-effectiveness claim. The Panel noted, however, that although Aubin *et al* post-dated O'Regan *et al*, there was no data to show that even if the later results had been added to the model used by O'Regan *et al* they would have changed the overall, broad conclusion that Champix was more cost-effective than NRT patches or bupropion. On the basis of the data before it the Panel ruled no breach of Clauses 7.2 and 7.3.

**4 Claim 'Favourable safety profile in approximately 4,000 treated smokers' and prescribing information**

The claim appeared on page 11 of the detail aid and was referenced to the Champix SPC.

## COMPLAINT

GlaxoSmithKline submitted that patient safety was paramount and the safety and tolerability page falsely reassured prescribers about the lack of serious events associated with Champix. A similar claim appeared on the key messages summary page. As highlighted in the recent Drug and Therapeutics Bulletin article using this type of wording did not give the reader a true picture of the safety issues surrounding Champix. The page did not make clear that there had been a number of reports of myocardial infarction (MI) as itemised in the Champix summary of product characteristics (SPC), and neither was this listed in the prescribing information. The Code clearly stated that the prescribing information should contain 'a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and warnings … giving, in abbreviated form, the substance of the relevant information in the summary of product characteristics, together with …'.

Whether or not a causal relationship had been established or the reports were infrequent or most patients had underlying risk factors, the EMEA required a statement about MI to be added to the side-effects section of the SPC. The EMEA concluded that 'the presence of cardiovascular risk factors cannot exclude the possibility of an additional contributory risk from the use of varenicline'. As such, the risk of MI should be included in the prescribing information as this was a serious side-effect. The fact that the MHRA had accepted Pfizer's rationale for not including MI in the prescribing information did not mean that there was not a breach of Clause 4.2. The prescriber was not able to make an informed appraisal of the medicine and as such this breached Clause 7.9.

## RESPONSE

Pfizer noted that section 4.8 of the SPC stated:

> 'Clinical trials included approximately 4,000 patients treated with CHAMPIX for up to 1 year (average exposure 84 days). In general, when adverse reactions 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 reactions.

In patients treated with the recommended dose of 1mg BID following an initial titration period the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation.

The treatment discontinuation rate due to adverse events 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% for 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).'

Based on both the treatment discontinuation rates reported in the clinical trial data, and the fact that when adverse reactions occurred their severity was generally mild to moderate, Pfizer considered that the claim 'Favourable safety and tolerability profile in approximately 4,000 treated smokers' was justified. Although nausea was the most common adverse effect of Champix it appeared to be generally well tolerated as only 2.7% of those experiencing nausea discontinued treatment. This rationale had recently been accepted by the MHRA which had accepted Pfizer's use of the claim 'Favourable safety and tolerability profile in approximately 4,000 treated smokers' in recent correspondence on this subject. Pfizer did not believe that the claim was in breach of Clause 7.9.

Pfizer noted GlaxoSmithKline's concern that reports of MI were not listed in the Champix prescribing information. However, Pfizer considered that it had taken all necessary steps to ensure that the Champix prescribing information was updated in a timely manner to include all safety information. The statement regarding post-marketing reports of MI was added to section 4.8 of the Champix SPC, effective July 2007:

– 'Post-marketing cases of myocardial infarction have been reported in patients taking varenicline.'

This information did not warrant inclusion within the table of very common, common, uncommon or rare side-effects outlined in section 4.8 of the SPC. No causal relationship between Champix and these cases of MI had been established. These reports were infrequent and most patients had additional pre-existing cardiovascular disease and/or other risk factors. In 2007 Pfizer thus took the view that the statement regarding post-marketing reports of MI did not warrant inclusion in the Champix prescribing information.

Subsequent reviews of the SPC had not led to any further changes to the information regarding MI. Therefore Pfizer still considered that inclusion in the prescribing information at this stage was not necessary. In recent correspondence the MHRA had agreed that Pfizer acted appropriately. Pfizer denied breaches of Clauses 4.2 or 7.9.

## PANEL RULING

The Panel noted that in July 2007 the statement 'Post marketing cases of myocardial infarction, depression and suicidal ideation have been reported in patients taking varenicline (see section 4.4)' had been added to the Champix SPC. The statement appeared beneath a table listing all adverse reactions which occurred at an incidence greater than placebo. Section 4.4 included additional information about depression and suicidal ideation but gave no additional information about MI. The prescribing information in the detail did not mention MI. A statement to see the SPC for less commonly reported side effects was included.

The Panel did not consider that in the circumstances the failure to include in the prescribing information the post marketing surveillance data in relation to MI meant that the prescribing information did not meet the requirements of Clause 4.2 that a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and contra-indications, relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of products characteristics, together with a statement that prescribers should consult the summary of products characteristics in relation to other side-effects be included. No breach of Clause 4.1 was ruled.

The Panel did not consider that the absence of information about MI on the page detailing the safety and tolerability of Champix, on the key messages page or in the prescribing information meant that the prescriber was not in a position to make an informed appraisal of the medicine. No breach of Clause 7.9 was ruled.

During its consideration of the case, the Panel noted that section 4.8 of the Champix SPC included the statement 'Clinical trials included approximately 4,000 patients treated with Champix for up to 1 year (average exposure 84 days). In *general*, [emphasis added] when adverse reactions occurred, onset was in the first week of therapy; severity was *generally* [emphasis added] mild to moderate and there were no differences by age, race or gender with regard to the incidence of adverse reactions'. In that regard the Panel queried whether the claim 'Favourable safety profile in approximately 4,000 treated smokers' was an accurate reflection of the SPC statement. The statement in the SPC appeared to be more qualified in tone than the claim in the detail aid. The Panel requested that Pfizer be advised of its concerns in this regard.

**Complaint received** **15 July 2008**

**Case completed** **29 August 2008**