CASE AUTH/2475/1/12

PFIZER v JOHNSON & JOHNSON

Nicorette Invisi Patch leavepiece

Pfizer complained about a leavepiece for Nicorette Invisi 25mg Patch (transdermal nicotine replacement therapy (NRT)) distributed by Johnson & Johnson. Nicorette Invisi 25mg Patch was indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who were unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them. Pfizer produced Champix (varenicline) which was indicated for smoking cessation.

The detailed response from Johnson & Johnson is given below.

A table compared a number of qualities of Nicorette Invisi Patch with those of varenicline. The quality 'Indicated as a Safer Option to Smoking' was followed by a green tick ('may be suitable') for the Invisi Patch and a red cross ('not recommended') for varenicline. Pfizer alleged that this implied that it was safer to continue smoking than to try to stop with varenicline. Pfizer alleged that the material was unbalanced, misleading, could not be substantiated, disparaged varenicline and did not demonstrate high standards. Pfizer further noted the statement below the table, 'The varenicline SPC [summary of product characteristics] states: "Care should be taken with patients with a history of psychiatric illness…"' but submitted that there were also a number of special warnings and precautions that were listed in the Nicorette Invisi Patch SPC. Pfizer alleged that data had therefore been 'cherry picked' from the SPCs. Pfizer alleged that the presentation of the information was again misleading, did not present a fair and balanced representation of the safety evidence available and did not demonstrate high standards.

The Panel considered that the table gave the misleading impression that the risk:benefit ratio for varenicline was such that it was safer to continue to smoke than try to quit with varenicline. A breach of the Code was ruled. The comparison of the two medicines was thus also misleading and a breach was ruled. The implication that varenicline was not indicated as a safer alternative to smoking was not capable of substantiation, disparaged varenicline and did not reflect the available evidence regarding the risk:benefit ratio. Breaches were ruled. The Panel considered that the material did not maintain high standards and ruled a breach of the Code. All of these rulings were appealed and in its consideration of the matter the Appeal Board noted the differences between the licensed indications for the medicines and Johnson & Johnson's submission that 'indicated' in the table had been used in its regulatory sense. According to the table, however, a green tick in the Invisi Patch column would be interpreted by the target audience as meaning the product 'may be suitable' as a safer option to smoking and a red cross for varenicline would inevitably be interpreted as meaning the opposite. The Appeal Board considered that the table was misleading as alleged and upheld all of the Panel's rulings.

Turning to the statement below the table that the varenicline SPC stated 'Care should be taken with patients with a history of psychiatric illness…', the Panel noted that this statement was taken from the varenicline SPC. The Panel also noted that although there were a number of warnings listed in the Nicorette Invisi 25mg Patch SPC, there was no warning in relation to use in patients with a history of psychiatric illness. The Panel considered that the statement about varenicline was not misleading with regard to the safety profile of either medicine and that it reflected the available evidence in relation to the use of the medicines in this patient population. No breaches of the Code were ruled including no breach in relation to the maintenance of high standards.

Pfizer alleged that to describe the safety profile of NRT as 'excellent' over-claimed the safety profile of the Invisi Patch in breach of the Code. A bar chart entitled 'Adverse drug reactions in an independent study comparing NRT (all forms) and varenicline', referenced to Stapleton *et al* (2008), depicted a selection of 'adverse drug reactions' from the study. Pfizer stated that with no description of the study design, readers might assume that this was a randomised, head-to-head, clinical trial comparison between NRT and varenicline rather than an observational, non randomised, cohort study which compared a group of patients taking NRT prior to the availability of varenicline, with a different group of patients who were treated with varenicline immediately post-launch. The reporting of adverse events in these cohorts could not imply causality (the term 'adverse drug reactions' should not be used) and the reporting rate for varenicline was likely to be influenced by the proximity to launch. Pfizer alleged that the bar chart was misleading and did not fully describe the design or the findings of the study. It did not allow readers to fully assess the data presented. The safety comparisons made could not be robustly substantiated by Stapleton *et al* and high standards had not been maintained, in breach of the Code.

The Panel noted that the bar chart was on a page headed 'NRT is well tolerated and has an excellent safety profile'. The depicted study, Stapleton *et al*, was concluded before the Nicorette Invisi 25mg Patch was first authorized in December 2008.

The Panel noted Johnson & Johnson's submission that the page at issue was about the safety and tolerability of NRT in general, and not Nicorette

compared with varenicline. The Panel considered, however, that the majority of readers would assume that the results shown in the bar chart were from a comparison of the Invisi Patch with varenicline. This impression was strengthened by the claim below the bar chart 'The favourable safety and tolerability profile of Nicorette has been shown in more than 100 clinical studies'.

The Panel noted that when varenicline was introduced in to the study detailed in Stapleton *et al* it would have been a new medicine. In this regard the Panel considered that patients were more likely to report possible adverse effects with it.

The Panel noted its concerns about the design and timing of the Stapleton study in relation to the availability of the medicines concerned. Within a Nicorette Invisi 25mg Patch leavepiece, the heading 'NRT is well tolerated and has an excellent safety profile' would be read as a claim for Nicorette Invisi 25mg Patch. The Panel considered that Stapleton *et al* did not support such a claim and in that regard the properties of the Invisi Patch had not been presented objectively. A breach of the Code was ruled.

With regard to the bar chart the Panel considered that for the reasons described above in relation to Stapleton *et al* the comparisons depicted were misleading with regard to the Nicorette Invisi 25mg Patch and varenicline. Breaches of the Code were ruled which were upheld on appeal. The bar chart did not present data in such a way as to give a clear and balanced view of the safety profile of either product and the Panel ruled a breach of the Code. As Nicorette Invisi 25mg Patch was not available at the time of the Stapleton *et al* evaluation, the Panel did not consider that the incidence of side-effects presented in the bar chart were capable of substantiation in relation to Nicorette Invisi 25mg Patch. Breaches of the Code were ruled which were upheld on appeal. The Panel considered that the use of the Stapleton *et al* data in this way amounted to a failure to maintain high standards and ruled a breach of the Code which was upheld on appeal.

The back page of the leavepiece was headed 'Nicorette Invisi 25mg Patch – Designed for first line recommendation'. Under a sub-heading 'Designed for tolerability' was the bullet point 'Well tolerated with an excellent safety profile' which was referenced to Tønnesen *et al* (1999). The Panel noted that the treatment used in this study was Nicorette 10mg and 15mg patches and not the Nicorette Invisi 25mg Patch, although some patients received 25mg of nicotine by using both the 15mg and 10mg patches at the same time. The authors concluded that NRT appeared to have few side-effects.

The Panel noted that from the list of six possible adverse events given in the Nicorette Invisi 25mg Patch SPC, one was very common (itching), three were common (dizziness/headache, gastrointestinal discomfort/nausea/vomiting and erythema), two were uncommon (palpitations and urticaria) and one was very rare (reversible atrial fibrillation). The SPC also stated that about 20% of Nicorette Invisi Patch users experienced mild local skin reactions during the first weeks of treatment. The SPC stated that at recommended doses the Nicorette Invisi 25mg Patch had not been found to cause any serious adverse effects. The Panel noted that the claim at issue appeared on the final page of the leavepiece and summarized the data within. The Panel noted its rulings above of breaches of the Code in relation to misleading safety comparisons within the leavepiece. The Panel considered that the claim was not a fair summation of the safety data within which was misleading and thus overclaimed the safety profile of Nicorette Invisi 25mg Patch as alleged. A breach of the Code was ruled.

Pfizer Limited complained about a six page, gate folded leavepiece for Nicorette Invisi 25mg Patch (transdermal nicotine replacement therapy (NRT)) (ref 06491) distributed to prescribers by Johnson & Johnson Limited. Nicorette Invisi 25mg patch relieved and/or prevented craving and nicotine withdrawal symptoms associated with tobacco dependence. It was indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who were unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them. Pfizer produced Champix (varenicline) which was indicated for smoking cessation.

The leavepiece, which was no longer in use, had been used and left with prescribers at the end of a product detail.

1 Page comparing Nicorette Invisi 25mg Patch with varenicline

COMPLAINT

Pfizer noted that one page of the leavepiece, entitled 'Nicorette Invisi 25mg Patch - Designed for versatility' with the sub-heading 'Suitable for a wide range of patient situations', featured a table which compared a number of qualities of Nicorette Invisi Patch with those of varenicline. The quality 'Indicated as a Safer Option to Smoking' was followed by a green tick for the Invisi Patch and a red cross for varenicline. Pfizer acknowledged that although the Invisi Patch was indicated as a safer alternative to smoking, the presentation of the information in the table was such as to suggest that the use of varenicline was not a safer alternative to smoking and imply that it was safer to continue smoking than to try to stop with varenicline. Pfizer alleged that the material was unbalanced, misleading, could not be substantiated, disparaged varenicline and did not demonstrate high standards in breach of Clauses 7.2, 7.3, 7.4, 7.9, 8.1 and 9.1.

Pfizer further noted that below the table was the statement 'The varenicline SPC [summary of product characteristics] states: "Care should be taken with patients with a history of psychiatric illness…"'. Whilst this wording was in Section 4.4 (Special warnings and precautions for use) of the varenicline SPC, there were also a number of special warnings

and precautions that were listed in the Nicorette Invisi Patch SPC. For example, caution in underlying cardiovascular disease, diabetes mellitus, phaeochromocytoma and uncontrolled hyperthyroidism had not been included on this page of the leavepiece. Pfizer alleged that data had therefore been 'cherry picked' from the SPCs, that the presentation of the information was again misleading, that it did not present a fair and balanced representation of the safety evidence available and did not demonstrate high standards in breach of Clauses 7.2, 7.9 and 9.1.

RESPONSE

Johnson & Johnson submitted that the table at issue was intended to allow prescribers to review and compare situations and patient groups where Nicorette Invisi Patch or varenicline would be appropriate. It was drawn from Sections 4.1, Therapeutic indications, 4.3, Contraindications, 4.6, Pregnancy and lactation and 4.7, Effects on ability to drive and use machines, of the SPCs. Johnson & Johnson considered it was a fair reflection of the situations where the two products might or might not be appropriate for use.

The indication section of the Nicorette Invisi 25mg Patch SPC stated: 'It is indicated to aid smokers who wish to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them' (emphasis added). Johnson & Johnson submitted that 'safer alternative to smoking' was a specific indication. It did not simply mean that using the product was safer than smoking, it meant that it could be used when the smoker did not intend to quit but wished to reduce risk to themselves or those around them. By contrast, varenicline did not include this specific indication. Johnson & Johnson submitted that it had expressed this as 'safer option to smoking' rather than 'safer alternative to smoking' in its communications because although the two phrases meant the same, 'a safer option' communicated the nature of the indication clearly and accessibly. The word 'indicated' was specifically included in the description to make this meaning clear and to avoid any doubt.

Johnson & Johnson did not consider that placing a tick against its indication in the table was unbalanced, misleading, could not be substantiated, disparaged varenicline or failed to demonstrate high standards and thus denied breaches of Clauses 7.2, 7.3, 7.4, 7.9, 8.1 and 9.1.

In relation to the statement 'Care should be taken with patients with a history of psychiatric illness…', Johnson & Johnson submitted that this was a direct and accurate quote from the varenicline SPC. It was a topic which had received considerable publicity, had been the subject of a CHM (Commission on Human Medicines) labelling change and was sufficiently important to be included in the comparison between NRT and varenicline. It was not included to mislead, present an unbalanced picture or to disparage varenicline. Varenicline was a licensed medicine and as such had a positive risk:benefit ratio and an established place in smoking cessation. The page in question was intended to allow the prescriber to think about situations where use of the medicine might be more or less appropriate, and clearly a history of psychiatric illness was a relevant consideration for prescribers.

Johnson & Johnson did not consider that the inclusion of this claim was misleading or failed to present a fair balanced representation of safety evidence or that it failed to demonstrate high standards, and in its view it did not breach Clauses 7.2, 7.9 or 9.1.

PANEL RULING

The Panel noted that in the table comparing various qualities of the Invisi Patch with those of varenicline, the quality 'Indicated as a Safer Option to Smoking' had a green tick in the Nicorette column and a red cross in the varenicline column. Below the table it was stated that the red cross indicated that the medicine was not recommended and the green tick that the medicine might be suitable. The Panel considered that the impression given by the table was that the risk:benefit ratio for varenicline was such that it was safer to continue to smoke than try to quit with varenicline. The Panel noted that varenicline was indicated for smoking cessation in adults and thus considered that the information given about varenicline was misleading. A breach of Clause 7.2 was ruled. The comparison of the two medicines was thus also misleading and a breach of Clause 7.3 was ruled. The implication that varenicline was not indicated as a safer alternative to smoking was not capable of substantiation and the Panel ruled a breach of Clause 7.4. The Panel considered that implying that varenicline was not indicated in smoking cessation and that continuing to smoke was safer than trying to quit with varenicline disparaged the medicine and it thus ruled a breach of Clause 8.1. The Panel noted that Clause 7.9 required that information and claims about side-effects reflect available evidence or be capable of substantiation by clinical experience. Insomuch as the table implied that it was safer to continue to smoke than take varenicline, the Panel considered that it did not reflect the available evidence regarding the risk:benefit ratio. A breach of Clause 7.9 was ruled. The Panel considered that the material did not maintain high standards and ruled a breach of Clause 9.1. All the above rulings were appealed by Johnson & Johnson.

Turning to the statement below the table that the varenicline SPC stated 'Care should be taken with patients with a history of psychiatric illness…', the Panel noted that this statement was taken from Section 4.4 of the varenicline SPC, Special warnings and precautions for use. The Panel also noted that although there were a number of warnings listed in Section 4.4 of the Nicorette Invisi 25mg Patch SPC, there was no warning in relation to use in patients with a history of psychiatric illness. In the Panel's view, it was also important to note that patients

using the Invisi Patch were already exposed to nicotine given their use of cigarettes. In that regard they had already had to manage the combined effects of nicotine and the conditions listed in Section 4.4 of the Invisi Patch SPC. The Panel did not consider that the statement about varenicline was misleading with regard to the safety profile of either medicine and ruled no breach of Clause 7.2. The statement reflected the available evidence in relation to the use of the medicines in this patient population and no breach of Clause 7.9 was ruled. The Panel noted its ruling above and ruled no breach of Clause 9.1. These rulings were not appealed.

APPEAL BY JOHNSON & JOHNSON

Johnson & Johnson submitted that the leavepiece entitled 'Designed for tolerability' was intended to provide prescribers with relevant information regarding the safety and efficacy of Nicorette Invisi 25mg Patch and the situations in which it might be appropriate to consider prescribing it.

Johnson & Johnson noted that the heading on page 4 was 'Nicorette Invisi 25mg Patch, Designed for versatility' with a subheading 'Suitable for a wide range of patient situations'. The page featured a table which compared between Nicorette Invisi 25mg Patch and varenicline in terms of key indications, cautions and contraindications. The columns in the table were headed 'Nicorette Invisipatch' and 'Varenicline', and both headings referred to the respective SPCs. Row 5 of the table ('Indicated as a Safer option to Smoking') directly compared the licensed indications for the two medicines in terms of whether they were specifically indicated as a 'safer alternative to smoking'.

Johnson & Johnson submitted that critical to this case was an understanding of the indications for the two products, and the specific wording of these indications as set out in Section 4.1 of the respective SPCs.

Johnson & Johnson submitted that when NRT was first introduced as a licensed medicine in the late 1970s it was only indicated for smokers making an immediate and complete quit attempt ie giving up smoking completely, and using NRT for a defined period in order to manage nicotine withdrawal symptoms. In 2005 a Committee on Safety of Medicines working group advised that the indication should be widened to include cutting down smoking as a 'stepping stone' to quitting completely.

Johnson & Johnson submitted that there had since been further interest in novel strategies for the use of medicinal nicotine. These strategies included temporary abstinence, where the smoker wished to avoid harming others or was unable to smoke because they were in a no-smoking environment, and harm reduction, where the smoker was not ready to quit but wished to substitute some or all of their cigarettes with medicinal NRT, with no limit on duration of use. The harm reduction strategy was outlined and endorsed in a report by the Tobacco Advisory Group of the Royal College of Physicians in 2008 which recommended that 'Use of existing [NRT] products as a temporary substitute for smoking (for example, in the home), or as a long-term substitute for smoking by those unable to quit, also needs to be encouraged'.

Johnson & Johnson submitted that the first application received by the MHRA to extend the licensed indications to include a harm reduction element for NRT was for the Nicorette Inhalator. This application was reviewed and approved by the CHM and the conclusions published in a Public Assessment Report in December 2009. In addition, the working group recommended that a harm reduction element was appropriate for inclusion within the indications of all other currently authorised forms of NRT. The wording approved by the CHM to be included within the indications of all NRT products was as follows:

'(Name of NRT…) relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them.'

This wording had been included as part of the approved indications listed on the SPC for Nicorette Invisi 25mg Patch, however this was not an approved indication for varenicline, which was solely 'indicated for smoking cessation in adults'.

Johnson & Johnson submitted that essentially, the harm reduction indication allowed for 'open-ended' use of NRT for an undefined period, based on the premise that using NRT relieved nicotine withdrawal symptoms, and provided nicotine in a form which was safer than nicotine obtained through smoking tobacco. The expression 'Safer Option to Smoking' had been adopted to refer to this specific indication. The wording 'Indicated as a Safer Option to Smoking' which appeared in row 5 of the table was therefore a specific reference to the harm reduction indication, which was included in the approved indications for Nicorette Invisi 25mg Patch which was not an approved indication for varenicline, which was solely indicated for 'smoking cessation in adults'.

Johnson & Johnson noted that Pfizer had presented its case for six separate breaches of the Code within a single, short paragraph and that the complaints procedure was essentially an adversarial process in which the evidence to be taken into account came from the two parties and that the complainant had the burden of proving their complaint on the balance of probabilities. Given the very brief nature of Pfizer's allegations, and the lack of evidence and argument presented, Johnson & Johnson was surprised that the Panel regarded Pfizer's grounds for complaint as compelling when it had merely alleged, without any supporting argument or evidence, that the presentation of data in the table implied that the

use of varenicline was not safer than smoking. Johnson & Johnson did not believe that Pfizer had proved its complaint on the balance of probabilities.

Johnson & Johnson noted that in its ruling, the Panel agreed with Pfizer that the table implied that the risk:benefit ratio for varenicline was such that it was safer to continue to smoke rather than try to quit with varenicline. The wording of the ruling was critical. A breach of Clause 7.2 was ruled based on row 5 and 'thus the comparison of the two medicines was also misleading and a breach of Clause 7.3 was ruled.' In other words, the subsequent rulings were derived from the single, isolated consideration that row 5 implied that smoking was safer than varenicline.

Johnson & Johnson submitted that this ruling resulted from taking row 5 of the table out of context of the overall table and the additional text on the page, and that the ruling did not recognize the significant differences in approved indications between the two products. Three points were of paramount importance in considering potential breaches of the Code on this page:

1 The table directly compared certain key indications, cautions and contraindications of the two products in question, and did not compare either of the products with smoking

2 The approved therapeutic indications for Nicorette Invisi 25mg Patch were fundamentally different from varenicline

3 'Safer Option to Smoking' referred to a specific indication for Nicorette Invisi 25mg Patch which was not shared by varenicline.

Each row in the table highlighted a different aspect of Nicorette Invisi 25mg Patch and varenicline to help the prescriber make an informed decision in different patient types. These were 'Driving or operating complex machinery'; 'Hazardous activities'; 'Children or adolescents 12-18 years'; 'Pregnancy'; 'Indicated as a Safer Option to Smoking'; 'Chronic generalized dermatological disorders' and 'Hypersensitivity to the active ingredients'.

Johnson & Johnson noted that the Panel considered row 5 of the table first. Obviously, readers would not typically start at row 5 and therefore by doing so, the Panel indicated a higher prominence to this claim than would be afforded by typical readers. The Panel had therefore taken this specific comparison out of context to the remainder of the page. This challenged the overall impression of the comparisons in the table. However Johnson & Johnson also addressed the Panel's specific concerns as raised in the ruling.

Johnson & Johnson reiterated that row 5 was titled 'Indicated as a Safer Option to Smoking'. 'Indicated' clearly informed the prescriber that this referred to the approved indications as set out in Section 4.1 (Therapeutic indications) of the respective SPCs. The phrase 'Safer Option to Smoking' very closely reflected the wording in the approved indications for Nicorette Invisi 25mg Patch, which stated that the product was indicated '…as a safer alternative to smoking for smokers and those around them'; this phrase was synonymous with 'safer alternative to smoking'. Use of upper case letters in the phrase 'Safer Option to Smoking' further reinforced that this term denoted a specific indication, and that no attempt was being made to invite any more general comparison with smoking. Prescribing information on the back page included a clear description of the approved indications for Nicorette Invisi 25mg Patch, including the 'Safer alternative to smoking' indication.

Johnson & Johnson submitted that it was legitimate to compare the indications for the two products, which had a number of important differences. It was key to note that the table compared certain aspects of two products licensed for various indications to help smokers and did not make any comparisons between varenicline and smoking. The nature of the comparison was very clear, and was highlighted by the column headings ('Nicorette Invisipatch' and 'Varenicline'). It was difficult to see how prescribers could view this table as making a comparison between smoking and varenicline. Johnson & Johnson could not see how prescribers could believe the table implied that varenicline was more dangerous than smoking. Given that it was indicated for smoking cessation, and the fact that varenicline was one of the most widely prescribed medicines for smoking cessation, it was not credible that prescribers could infer that continuing to smoke was safer than attempting to quit with varenicline.

Johnson & Johnson submitted that in the context of the page heading, the subheading and the rest of the table, row 5 could only be seen as a direct, accurate and fair comparison of approved product indications, and not a comparison between varenicline and smoking. Johnson & Johnson submitted that it had never claimed directly or indirectly that varenicline was less safe than smoking in any sub-population. Johnson & Johnson had merely presented a valid and direct comparison of key indications, cautions and contraindications for Nicorette Invisi 25mg Patch and varenicline. Thus Johnson & Johnson contended that the table did not compare varenicline with an option to 'continue smoking' and did not imply that smoking was safer than taking varenicline. Johnson & Johnson appealed the ruling of a breach of Clause 7.2.

Johnson & Johnson appealed the Panel's ruling of a breach of Clause 7.3 noting that it was derived directly from the ruling of a breach of Clause 7.2 using the same overall argument about the relative safety of smoking and varenicline.

Johnson & Johnson noted that the Panel subsequently ruled a breach of Clause 7.4 because 'the implication that varenicline was not indicated as a safer alternative to smoking was not capable of substantiation'. In fact, it was a demonstrable fact that, unlike Nicorette Invisi 25mg Patch, varenicline was not specifically indicated as a safer alternative to

smoking. Therefore, Johnson & Johnson submitted that this claim was very clearly capable of substantiation, and it appealed the ruling of a breach of Clause 7.4.

Johnson & Johnson noted that the Panel further ruled a breach of Clause 8.1 for disparaging the medicine by 'implying that varenicline was not indicated in smoking cessation and that continuing to smoke was safer than trying to quit with varenicline'. Johnson & Johnson submitted that it had already made its arguments regarding the lack of positioning of varenicline against continuing to smoke and denied this interpretation. Nor could Johnson & Johnson find anything in the table that suggested that varenicline was not indicated for smoking cessation. Johnson & Johnson believed that as one of the most widely prescribed medicines for smoking cessation, prescribers would be well aware that varenicline was approved for this indication. Therefore Johnson & Johnson appealed the ruling of a breach of Clause 8.1 noting its concern that this breach was ruled partly on the grounds that the table implied varenicline was not indicated for smoking cessation, even though Pfizer had not alleged this specific point in its complaint.

Johnson & Johnson noted that the Panel then ruled a breach of Clause 7.9 for failing to represent properly the safety profile of varenicline on the grounds that the table portrayed varenicline as more dangerous than continuing smoking. The safety profile of varenicline was presented in accordance with the SPC and did not in any way imply that smoking was a safer option than taking varenicline. Johnson & Johnson therefore appealed the ruling of a breach of Clause 7.9.

Johnson & Johnson submitted that on the basis of row 5 in the table, the Panel ruled five separate breaches of the Code and then concluded that the overall presentation was such as to have breached high standards and ruled a breach of Clause 9.1. Johnson & Johnson appealed this ruling on the grounds that the five previous rulings were not valid. Even if the Appeal Board upheld some of the rulings, Johnson & Johnson did not believe that the overall presentation on this page represented a breach of high standards.

COMMENTS FROM PFIZER

Pfizer noted that Johnson & Johnson's appeal was focused on the approved indications for the two products, and the specific wording within these indications as set out in Section 4.1 of the respective SPCs. A brief history of the harm reduction campaign was also provided. Whilst this was informative, it did not justify the inappropriate portrayal and comparison of Nicorette Invisi 25mg Patch and varenicline in the table in question.

Pfizer alleged that it was not clear from the table that 'indication' had been referred to, using the regulatory definition of this word. A GP or smoking cessation specialist, for example, might not be familiar with such terminology. To state 'indicated as a safer option to smoking' could easily infer that the patch was a safer option to smoking and the opposite was so for varenicline. This was compounded by the simple 'tick' and 'cross' presentation. Johnson & Johnson argued that the comparison was only between the patch and varenicline, and not between the treatment and smoking. However, 'a safer option to smoking' invited a direct comparison on safety grounds between the treatment and smoking.

Pfizer alleged that whilst Johnson & Johnson had referred to a report by the Tobacco Advisory Group of the Royal College of Physicians in 2008 which recommended that 'Use of existing (NRT) products as a temporary substitute for smoking (for example, in the home), or as a long-term substitute for smoking by those unable to quit, also needs to be encouraged', this was substantially different to stating, with no context, 'indicated as a safer option to smoking'. Pfizer maintained that the material was unbalanced, misleading in relation to the safety of varenicline and the comparison being claimed, could not be substantiated, disparaged varenicline and did not demonstrate high standards of promotional practice. Pfizer alleged therefore that the material in question was in breach of Clauses 7.2, 7.3, 7.4, 7.9, 8.1 and 9.1.

APPEAL BOARD RULING

The Appeal Board noted the differences between the licensed indications for the two medicines. The Nicorette Invisi 25mg Patch indications included use as a safer alternative to smoking for smokers and those around them whereas varenicline was only indicated for smoking cessation in adults. The Appeal Board further noted Johnson & Johnson's submission that 'indicated' in row 5 of the table had been used in its regulatory sense. The green tick in the Invisi Patch column however, according to the key to the table meant 'may be suitable'. In the Appeal Board's view the target audience would not be familiar with the regulatory use of 'indicated' and would, given the key to the table, interpret row 5 to mean that Nicorette Invisi 25mg Patch could be used as a safer option to smoking. A red cross for varenicline would inevitably be interpreted as the opposite. The red cross in the table was stated to denote 'not recommended' and in that regard the Appeal Board noted that the phrase 'not recommended' had not been used in its regulatory sense.

The Appeal Board did not accept the submission that the table was a fair comparison of the approved product indications. The Appeal Board considered that the table suggested that varenicline was not a safer alternative to smoking as alleged and in that regard it upheld the Panel's rulings of breaches of Clauses 7.2, 7.3, 7.4, 7.9, 8.1 and 9.1. The appeal on all points was unsuccessful.

2 Page comparing NRT with varenicline

COMPLAINT

Pfizer referred to a page of the leavepiece entitled 'NRT is well tolerated and has an excellent safety profile'. Pfizer considered that use of the word 'excellent' in the description of the NRT safety profile on this page of the leavepiece and on the back page of the leavepiece was not appropriate. Nicorette Invisi 25mg Patch had adverse effects, warnings and precautions and contraindications which were listed in its SPC. Pfizer alleged that the word 'excellent' was an inappropriate adjective to use in this context, which over-claimed the safety profile of the Invisi Patch in breach of Clause 7.10.

A bar chart on the page at issue, entitled 'Adverse drug reactions in an independent study comparing NRT (all forms) and varenicline', was referenced to Stapleton *et al* (2008) and depicted a selection of 'adverse drug reactions' from the study. Pfizer stated that as there was no description of the study design, readers might assume that this was a randomised, head-to-head, clinical trial comparison between NRT and varenicline rather than an observational, non randomised, cohort study which compared a group of patients taking NRT prior to the availability of varenicline, with a different group of patients who were treated with varenicline immediately post-launch. The reporting of adverse events in these cohorts could not imply causality (the term 'adverse drug reactions' should not be used) and the reporting rate for varenicline was likely to be influenced by the proximity to launch. Pfizer did not consider it was appropriate to compare the safety information from these two distinct, non randomised, open label, observational cohorts in this way in promotional material. Furthermore, a primary objective of the study was to compare the clinical effectiveness of NRT vs varenicline in terms of quit rate. This was significantly higher in the varenicline group. Pfizer considered that fair balance would require both efficacy and safety to be shown. None of the above information was made clear on the page and hence readers were misled as to the nature and limitations of the data being presented. Pfizer alleged that the bar chart was therefore misleading and did not fully describe the design or the findings of the study. It did not allow readers to fully assess the data presented. The safety comparisons made could not be robustly substantiated by Stapleton *et al* and high standards had not been maintained, in breach of Clauses 7.2, 7.3, 7.4, 7.8, 7.9 and 9.1.

RESPONSE

Johnson & Johnson submitted the page at issue was not about Nicorette, but rather about the safety and tolerability of NRT in general compared with varenicline. The page accurately and comprehensively reflected safety data from the only published study which compared varenicline with various NRT options.

Johnson & Johnson submitted that, grammatically, 'excellent' was an adjective and not a superlative as asserted. As such it might be used as long as it could be substantiated. The company acknowledged that 'excellent' could rarely be supported when describing the safety profile of a medicine but in this case it considered it was justified and its use was accepted when Invisi Patch materials were pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA).

Johnson & Johnson submitted that the safety profile of NRT was well established and its status as a non-prescription medicine reflected the fact that it was very well tolerated, adverse events were usually mild and transient and serious adverse drug reactions were unlikely. In fact NRT was freely available from most retail outlets without pharmacist supervision. Johnson & Johnson also noted that smokers were already routinely exposed to nicotine and were well used to 'titrating' their nicotine intake to avoid adverse effects. In addition the safety profile of nicotine was such that nicotine-containing products (such as electronic cigarettes) were available as unregulated non-medicinal products. Johnson & Johnson did not consider this would be the case if the safety profile of nicotine was not considered to be excellent.

Johnson & Johnson stated that the leavepiece was aimed at prescribers whose frame of reference was likely to be prescription medicines. It considered that in this context it was reasonable to state that the product was 'well tolerated' and had an 'excellent safety profile'. Johnson & Johnson noted that many people who quit smoking suffered from withdrawal symptoms which might often be confused with adverse events.

Johnson & Johnson submitted that NRT was used by patients who had already been using nicotine in a much more harmful format as evidenced by the statement in the Invisi Patch SPC 'Any risks that may be associated with NRT are substantially outweighed by the well established dangers of continued smoking'.

The description 'excellent' appeared above a bar chart in which the side effect profiles for NRT and varenicline were presented. These data were taken from Stapleton *et al* which directly compared varenicline with NRT and Johnson & Johnson considered provided complete context for the claim. Given this, the company did not consider the claim misleading. A direct quotation from Stapleton *et al* was also relevant as it described the side effect profile as 'benign', a term which Johnson & Johnson considered, when applied to safety, equated with 'excellent':

'Nicotine replacement therapy (NRT) has become the standard pharmacological treatment for tobacco dependence, due to its well-proven effectiveness, benign side effect profile and easy availability through pharmacy and general sales.'

Johnson & Johnson considered that smoking cessation experts would also agree that NRT had an excellent safety profile as illustrated by the following quotation from the Oxford Textbook of Primary

Medical Care: 'However, many clinicians consider NRT to be the first line drug treatment for nicotine dependence because of its excellent safety profile.'

Johnson & Johnson considered that as those who used NRT had already been exposed to nicotine, combined with the long established benign safety profile of NRT and the availability of nicotine in non-prescription medicines and even non-medicinal products, made nicotine a unique active ingredient and justified the use of 'excellent' to describe its safety profile. The company consider that the use of the word to be appropriate and that it did not breach Clause 7.10.

Johnson & Johnson considered that the data from Stapleton *et al* were reflected accurately in the bar chart and therefore not misleading. Pfizer had asserted that readers might assume this was a randomised, head-to-head clinical trial comparison as it was not specifically stated that it was an observational study. Johnson & Johnson did not consider this was necessarily the case. Many types of data were presented to prescribers including randomised studies, observational studies, case controlled studies etc. Prescribers understood this and no assertion was made that these data were from a randomised study.

Johnson & Johnson noted Pfizer's assertion that the term 'adverse drug reactions' should not be used. Johnson & Johnson submitted that it had used this term as the authors had used it as a section heading when describing these occurrences. The table from which the data were taken also described them as 'adverse drug symptoms'. The details of the assessment of these reports were not given in detail in the paper. However, Johnson & Johnson submitted that the patients were asked to report suspected adverse drug reactions and the company stated that it reflected that in its description. The authors only tabulated terms which were reported significantly more frequently in one group compared with the other.

Johnson & Johnson noted Pfizer's assertion that the safety data should not have been used from Stapleton *et al* unless efficacy data were also included in order to give a balanced comparison. Johnson & Johnson submitted that there was no requirement to provide safety and efficacy data for every clinical paper which was included in a detail aid. This page was about the safety and tolerability of NRT and there was no requirement when presenting data from a study to present data from all the outcomes considered. The efficacy of the medicines was not in question and not relevant to this particular page of the detail aid.

Johnson & Johnson considered that the bar chart was not misleading and adequately presented a clear, fair and balanced view of the data. The adverse drug reaction data were presented in full and accurately tabulated from the original paper allowing readers to fully assess of the data presented. The company considered that it was appropriate to use Stapleton *et al* to illustrate the safety profile of NRT and that these data would help a prescriber to make a prescribing decision. It did not consider that it had failed to maintain high standards and considered it had not breached Clauses 7.2, 7.3, 7.4, 7.8, 7.9 or 9.1.

PANEL RULING

The Panel noted that Pfizer had referred to two uses of the word 'excellent' to describe the safety profile of the Invisi Patch – on a page headed 'NRT is well tolerated and has an excellent safety profile' and in a bullet point on the back page. The Panel considered the two pages separately.

The heading 'NRT is well tolerated and has an excellent safety profile' was on a page which featured a bar chart adapted from Stapleton *et al*. Stapleton *et al* had compared the adverse drug reactions of varenicline (n=208) and NRT (n=204) by asking patients to report 'any unpleasant effects you think [the medicine] may have caused'. Those using NRT could choose between all licensed preparations and doses; 60% used a nicotine patch, 25% a nasal spray, 11% gum or lozenge and 5% an inhaler or microtab. The study was conducted between May 2006 and April 2007. The Nicorette Invisi 25mg Patch was first authorized in December 2008.

The Panel noted Johnson & Johnson's submission that the page at issue was about the safety and tolerability of NRT in general, and not Nicorette compared with varenicline. The Panel considered, however, that the majority of readers would assume that the results shown in the bar chart were from a comparison of the Invisi Patch with varenicline. This impression was strengthened by the claim below the bar chart 'The favourable safety and tolerability profile of Nicorette has been shown in more than 100 clinical studies'.

The Panel noted that in Stapleton *et al*, varenicline was introduced in the clinic conducting the study in January 2007 (8 months after the start of the study) after which a minority of patients chose to use NRT. Varenicline was first authorized in September 2006 and so when it was introduced in to the study it would have been a new medicine. In this regard the Panel considered that patients were more likely to report possible adverse effects with it. The bar chart showed statistically significantly greater incidences of most adverse drug reactions with varenicline than with NRT with the exception of skin irritation.

The Panel noted its concerns about the design and timing of the Stapleton study in relation to the availability of the medicines concerned. Within a Nicorette Invisi 25mg Patch leavepiece, the heading 'NRT is well tolerated and has an excellent safety profile' would be read as a claim for Nicorette Invisi 25mg Patch, supported by the Stapleton *et al* data immediately below. The Panel considered that Stapleton *et al* did not support such a claim for the Invisi Patch and in that regard the properties of the medicine had not been presented objectively. A breach of Clause 7.10 was ruled. This ruling was not appealed.

With regard to the bar chart the Panel considered that for the reasons described above in relation to Stapleton *et al* the comparisons depicted were misleading with regard to the Nicorette Invisi 25mg Patch and varenicline. Breaches of Clauses 7.2 and 7.3 were ruled. This ruling was appealed by Johnson & Johnson. The bar chart did not present data in such a way as to give a clear and balanced view of the safety profile of either product and the Panel ruled a breach of Clause 7.8. This ruling was not appealed. As Nicorette Invisi 25mg Patch was not available at the time of the Stapleton *et al* evaluation, the Panel did not consider that the incidence of side-effects presented in the bar chart were capable of substantiation in relation to Nicorette Invisi 25mg Patch, and ruled breaches of Clauses 7.4 and 7.9. This ruling was appealed by Johnson & Johnson. The Panel considered that the use of the Stapleton *et al* data in this way amounted to a failure to maintain high standards and ruled a breach of Clause 9.1. This ruling was appealed by Johnson & Johnson.

With regard to the back page of the leavepiece, this was headed 'Nicorette Invisi 25mg Patch – Designed for first line recommendation'. Under a sub-heading 'Designed for tolerability' was the bullet point 'Well tolerated with an excellent safety profile' which was referenced to Tønnesen *et al* (1999). This reported the Collaborative European Anti-Smoking Evaluation (CEASE) trial, which was a multicentre, randomized, double-blind, placebo controlled smoking cessation study comparing different doses and treatment durations of NRT. The Panel noted that the treatment used in this study was Nicorette 10mg and 15mg patches, and not the Nicorette Invisi 25mg Patch, although some patients received 25mg of nicotine by using both the 15mg and 10mg patches at the same time. Other patients received either the 15mg patch or placebo. Tønnesen *et al* noted that the overall incidence of adverse events was low and these were generally transient. Nausea/vomiting were the only reported symptoms with a higher frequency in the 25mg group (7.3%) compared with the 15mg group (5.4%); these adverse events were more common in both active treatment groups than in the placebo group (3.7%, $p<0.05$). Headache was reported in 5.6% of the 25mg group, 5.3% of the 15mg group and 3.9% of the placebo. The incidence of insomnia was 4.9%, 5.4%, and 5.9% respectively. Palpitations and tachycardia were reported by 2.25% (25mg), 2.6% (15mg) and 0.9% (placebo). Frequencies of nightmares during the first week of treatment were 8% (25mg), 7% (15mg) and 6% (placebo), compared with 7%, 8% and 7%, respectively, for the week preceding the start of treatment. The figures for vivid dreams were 20% (25mg), 18% (15mg) and 15% (placebo), compared with 18%, 19% and 17% before starting treatment. The authors stated that nightmares and vivid dreams were collected using a checklist, which they considered might explain the high frequency. Local adverse events comprised itching (25mg 14.4%, 15mg 12.9% and placebo 5%) and rash (25mg 5.2%, 15mg 5.2% and placebo 3.5%) in the patch area. Two per cent of subjects discontinued treatment due to adverse events in both the active and placebo groups. There were four myocardial infarctions during the study period which were within the expected range. The authors concluded that NRT appeared to have few side-effects.

The Panel noted the side-effects reported by Tønnesen *et al* and that night time awakenings/sleep disturbances were possible symptoms of nicotine withdrawal. The Panel also noted that from the list of six possible adverse events given in Section 4.8 of the Nicorette Invisi 25mg Patch SPC, one was very common (itching), three were common (dizziness/headache, gastrointestinal discomfort/nausea/vomiting and erythema), two were uncommon (palpitations and urticaria) and one was very rare (reversible atrial fibrillation). The SPC also stated that about 20% of Nicorette Invisi Patch users experienced mild local skin reactions during the first weeks of treatment. The SPC stated that at recommended doses the Nicorette Invisi 25mg Patch had not been found to cause any serious adverse effects. The Panel noted Johnson & Johnson's submission about the prior exposure of patients to nicotine, the long established benign safety profile of NRT and the availability of nicotine in non-prescription medicines. The Panel noted that the claim at issue appeared on the final page of the leavepiece and summarized the data within. The Panel noted its rulings above of breaches of the Code in relation to misleading safety comparisons within the leavepiece. The Panel considered that the claim was not a fair summation of the safety data within which was misleading and thus overclaimed the safety profile of Nicorette Invisi 25mg Patch as alleged. A breach of Clause 7.10 was ruled. This ruling was not appealed.

APPEAL BY JOHNSON & JOHNSON

Johnson & Johnson submitted that page 5 of the leavepiece was intended to illustrate the safety profile of all forms of NRT compared with varenicline. All forms of NRT were shown as the comparator because there were no published data directly comparing varenicline and Nicorette Invisi 25mg Patch. The page was entitled 'NRT was well tolerated and has an excellent safety profile'. Data was presented as a bar chart derived accurately and comprehensively from Stapleton *et al*. The bar chart showed the incidence of adverse reactions experienced by patients using NRT or varenicline and included the ten terms reported with a statistically significantly greater frequency in one group or the other. This page was intended to deal solely with safety and tolerability and not efficacy.

Johnson & Johnson submitted that the contested breaches on this page were ruled on a simple misinterpretation of presentation. Pfizer had alleged several breaches of the Code on page 5:

- inadequate information was provided about the study design
- the term 'adverse events' should have been used rather than 'adverse reactions'
- the study design was inherently biased
- efficacy data from the study should also have been presented for balance.

Johnson & Johnson noted that Pfizer had alleged that for these reasons, page 5 of the leavepiece was misleading and did not fully describe the design or findings of the study and did not allow readers to fully assess the data presented. Breaches of Clauses 7.2, 7.3, 7.4, 7.8, 7.9 and 9.1 were alleged.

Johnson & Johnson noted that the Panel had acknowledged the deficiencies of the study design. However, it was clear from the following extracts from the Panel's ruling that it was made upon a different basis.

'The Panel considered, however, that the majority of readers would assume that the results shown in the bar chart were from a comparison of the Invisi Patch with varenicline'

'With regard to the bar chart the Panel considered that for the reasons described above in relation to Stapleton *et al* the comparisons depicted were misleading with regard to the Nicorette Invisi 25mg Patch and varenicline'

Johnson & Johnson submitted that despite no such allegation from Pfizer, the Panel concluded that prescribers would assume that the results shown in the bar chart were from a comparison of the Nicorette Invisi 25mg Patch with varenicline. As a result the Panel ruled breaches of all six clauses. Johnson & Johnson appealed the ruling on this specific point which it was clear formed the basis of the Panel's rulings.

Johnson & Johnson submitted that a potential sources of bias existed within all studies. The possible existence of bias in a study could not therefore preclude the use of such studies in promotional material, especially where they were the best comparison available. Nor did Johnson & Johnson believe that the adverse reaction profile for varenicline demonstrated Stapleton *et al* was inherently flawed as it was generally consistent with the varenicline SPC. Apart from one prospective study with a patch which was neither manufactured by Johnson & Johnson nor the same strength as the Nicorette Invisi Patch, Stapleton *et al* was the only study which compared the safety profile of any NRT product with varenicline. Furthermore, prescribers would value an insight into the safety profiles of NRT and varenicline which had been gathered from a study of routine therapeutic use.

In hindsight Johnson & Johnson acknowledged that the bar chart would have presented a more complete picture if it had been accompanied by further information on the study design and methodology and so it had accepted the ruling of a breach of Clause 7.8. However it did not see how it could have been made clearer that the bar chart represented NRT rather than Nicorette Invisi Patch, and it contended that it was valid and helpful for the prescriber to provide data from a comparison with all forms of a chemical entity where no comparison was available with a specific formulation.

Johnson & Johnson submitted that it was clearly stated three times on page 5 that the data related to NRT in general rather than any specific form or brand. The page heading clearly indicated that this was a depiction of the tolerability of NRT overall. The bar chart featured on the page was clearly headed 'Adverse drug reactions in an independent study comparing NRT (all forms) and varenicline.' In addition, the key to the bar chart stated 'NRT (n=204)'. In contrast to the other pages within the leavepiece, there was no mention in the page heading or anywhere else on the page of the specific product Nicorette Invisi Patch. The word Nicorette appeared once, below the bar chart in a separate claim and the use of the Nicorette brand name rather than the Nicorette Invisi 25mg Patch product name clearly indicated that this was a brand and not a formulation-specific claim.

Johnson & Johnson submitted that it was therefore abundantly clear that the intention of the page and the chart was to consider the safety profile of NRT in general, rather than any specific form and/or brand of NRT. In its complaint, Pfizer acknowledged that the reader would assume this was a comparison between NRT and varenicline, and Pfizer alleged that prescribers would assume that the bar chart compared Nicorette Invisi Patch with varenicline. Johnson & Johnson again noted that the burden of proof rested with the complainant, and that the evidence taken into account should come from the complainant and the respondent. However, in this case the Panel had ruled multiple breaches on a pivotal argument that was never presented by Pfizer.

Johnson & Johnson submitted that it was important to note that the target audience was very familiar with the various forms of NRT and the various formulations of Nicorette specifically. It was highly unlikely that a typical prescriber would conclude, as the Panel had done, that the bar chart presented Nicorette Invisi 25mg Patch data specifically.

The Panel's interpretation that the bar chart portrayed Nicorette Invisi 25mg Patch specifically had led to several rulings of breaches of the Code which Johnson & Johnson submitted were unreasonable and incorrect.

Johnson & Johnson noted that the Panel ruled breaches of Clauses 7.2 and 7.3 in that the bar chart misrepresented a comparison between Nicorette Invisi 25mg Patch and varenicline. Johnson & Johnson appealed these rulings. The product name 'Invisi 25mg Patch' did not appear anywhere on the page, and three separate references to 'NRT' made it clear to the prescriber that the data presented referred to NRT in general.

Johnson & Johnson submitted that on the basis that the Nicorette Invisi 25mg Patch was not launched at the time of Stapleton *et al*, the Panel ruled breaches of Clause 7.4 in that the study failed to substantiate the claims for Nicorette Invisi 25mg Patch and of Clause 7.9 in that it misrepresented the safety profile of Nicorette Invisi 25mg Patch. Johnson & Johnson

submitted that as stated above, there was no specific reference to Nicorette Invisi 25mg Patch on the page in question which depicted all forms of NRT. Therefore Johnson & Johnson could not see how it could be held in breach for either clause. The bar chart accurately depicted the data presented in Stapleton *et al* and was therefore capable of substantiation. No attempt had been made on the page to present safety information on Nicorette Invisi 25mg Patch, and so the safety profile of Nicorette Invisi 25mg Patch could not possibly have been misrepresented.

Johnson & Johnson submitted that the combined interpretation of the rulings was such that the Panel then considered that high standards had not been maintained and ruled a breach of Clause 9.1. Johnson & Johnson appealed this ruling on the grounds that the Panel had misunderstood the data presented in a way that a typical prescriber would not.

COMMENTS FROM PFIZER

Pfizer noted that Stapleton *et al* was an observational, non-randomised, cohort study which compared a group of patients taking NRT prior to the availability of varenicline, with a different group of patients who were treated with varenicline immediately post-launch. A breach of Clause 7.8 had been accepted by Johnson & Johnson as it acknowledged in hindsight that the bar chart would have presented a more complete picture if it had been accompanied by further information on the study design and methodology. In addition Johnson & Johnson had accepted breaches of Clause 7.10 through over-stating the safety profile of Nicorette Invisi 25mg Patch.

Pfizer considered, therefore, that it seemed that Johnson & Johnson had accepted two fundamental issues with this material. Pfizer alleged that as the exact nature of the data shown was not made clear to the reader the bar chart was misleading in breach of Clauses 7.2 and 7.3. It did not allow the reader to be fully informed about the data to make an evaluation of the medicines or a comparison of the medicines. Stapleton *et al* was not sufficiently robust to be able to make safety comparisons and claims between NRT (or Nicorette Invisi 25mg Patch) and varenicline because of the design limitations. Pfizer alleged that the safety comparisons could not be substantiated in breach of Clauses 7.4 and 7.9.

Pfizer alleged that taken together, high standards had not been demonstrated (in breach of Clause 9.1) by using this data to make safety and tolerability claims, which appeared to be the main purpose of the leavepiece which had the overarching claim on page 1 of 'Designed for Tolerability.' Pfizer alleged that page 5 of the leavepiece was in breach of Clauses 7.2, 7.3, 7.4, 7.9 and 9.1.

APPEAL BOARD RULING

The Appeal Board noted that the title of the bar chart referred to 'Adverse drug reactions'. Although this term was also used in Stapleton *et al*, the correct regulatory term was 'adverse drug events'.

The Appeal Board noted that Stapleton *et al* was an efficacy study and more patients gave up smoking with varenicline compared with NRT. In the Appeal Board's view many of the adverse events listed could have been symptoms of nicotine withdrawal and not adverse drug events *per se*. In that regard patients on varenicline would be expected to have a higher incidence of such symptoms than those taking NRT.

The Appeal Board noted Johnson & Johnson's submission that the page at issue was about the safety and tolerability of NRT in general, and not Nicorette compared with varenicline. However, the Appeal Board considered that in a Nicorette Invisi Patch leavepiece, which on a previous page had compared Nicorette Invisi Patch with varenicline, readers would assume 'NRT (all forms)' to have at the very least included data for Nicorette Invisi 25mg Patch which was not so. Nicorette Invisi 25mg Patch was not available over the time period covered by Stapleton *et al*.

The Appeal Board considered that the majority of readers would assume that the results shown in the bar chart were from a comparison of the Nicorette Invisi 25mg Patch with varenicline and this impression was strengthened by the claim below about Nicorette.

The Appeal Board considered that in relation to Stapleton *et al* the bar chart depicted a misleading comparison between Nicorette Invisi Patch and varenicline. The Appeal Board did not consider that the incidence of adverse events presented in the bar chart were capable of substantiation in relation to Nicorette Invisi Patch; high standards had not been maintained. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3, 7.4, 7.9 and 9.1. The appeal on all points was unsuccessful.

Complaint received **31 January 2012**

Case completed **21 June 2012**