CASE AUTH/2298/2/10

JOHNSON & JOHNSON/DIRECTOR v GLAXOSMITHKLINE CONSUMER HEALTHCARE

NiQuitin 21mg Clear Patch mailing

Johnson & Johnson complained about a mailing sent by GlaxoSmithKline Consumer Healthcare to promote NiQuitin 21mg Clear Patch (nicotine replacement therapy NRT)). The leaflet and a covering letter each bore the same reference and the date of preparation for both was December 2009. NiQuitin Clear was indicated for the relief of nicotine withdrawal symptoms including cravings as an aid to smoking cessation.

As possible breaches of the undertakings given in Cases AUTH/1253/11/01 and AUTH/1401/12/02 were alleged, that part of the case was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

The detailed responses from GlaxoSmithKline Consumer Healthcare are given below.

The six page, gate folded leaflet was entitled 'Which therapeutic nicotine patch delivers more nicotine faster than any other patch?' A diagonal flash on the front page referred to 'New data'.

Page 2 of the leaflet was headed 'From day one' followed by the claim 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch' which was referenced to Fant *et al* (2000) and data on file. Beneath, a graph showed comparative mean adjusted plasma nicotine concentrations from a single dose of NiQuitin 21mg patch or Nicorette 25mg patch over 32 hours. Data for the graph came from the data on file.

Johnson & Johnson alleged that the claim was ambiguous and misleading primarily due to lack of clarity relating to the measures of speed and extent of nicotine delivery upon which the claim was based. The reference to 'more' nicotine being delivered 'faster' with NiQuitin than with other patches could relate to higher and more rapid peak plasma level C_{max}, higher and more rapid total nicotine delivery (area under the curve (AUC)) or higher nicotine levels at every timepoint measured.

The data presented appeared to show that the C_{max} was higher and achieved more rapidly with the NiQuitin patch. However, it was not clear from the page whether the difference was statistically significant. Irrespective of the statistical significance, C_{max} was of little clinical relevance for nicotine patches which were designed to deliver sustained, steady plasma levels over an extended period. It might be that the data presented indicated that C_{max} was achieved more rapidly with the NiQuitin 21mg patch, but this was not the same as delivering 'more nicotine faster…'. C_{max} was not a measure of the amount of nicotine delivered but a snap shot of plasma levels at a one time point.

As the Nicorette 16 hour patch was intended to be removed after 16 hours it delivered its nicotine dose faster than the NiQuitin 21mg patch which was intended to be removed after 24 hours. Indeed, the NiQuitin patch would continue to deliver nicotine for eight hours after the Nicorette patch had been removed. The 'full therapeutic dose' of nicotine was thus delivered considerably quicker with the Nicorette patch than with the NiQuitin patch.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare had noted that NiQuitin Clear 21mg patch could be worn for 16 or 24 hours. Johnson & Johnson submitted that this might be true but the NiQuitin patch was clearly intended to be used for 24 hours. The summary of product characteristics (SPC) stated: 'NiQuitin Clear patches should be applied once a day … preferably soon after waking, and worn continuously for 24 hours … . Patches may be removed before going to bed if desired. However, use for 24 hours is recommended to optimise the effects against morning cravings'. Johnson & Johnson submitted that the vast majority of clinical evidence for the NiQuitin patch was from clinical studies of 24 hour usage.

As regards the AUC, this was a measure of the total amount of nicotine delivered. Therefore, Johnson & Johnson believed that this measure was of particular relevance to the claim at issue. In the context of a patch applied daily, the claim 'delivers more nicotine faster' could only reasonably be assumed to refer to the total delivery of nicotine as measured by AUC. Given that AUCs for the two patches would always be measured or calculated over a specific period (eg $AUC_{0\text{-}24}$), for the comparison to be fair this time should be the same for both patches. One patch could not deliver its measured AUC faster than another patch. Comparative AUCs could be higher but not faster.

Another possible interpretation of the claim was that NiQuitin 21mg Clear patch delivered a higher level of nicotine at each time point. This was not the case as levels were higher for the Nicorette 25mg patch at 12 and 14 hours.

Johnson & Johnson noted that GlaxoSmithKline Consumer Healthcare justified 'faster' and 'more' independently of each other. Even if these two individual statements were true, this did not mean

that the overall claim which linked the amount of nicotine delivered and speed of delivery could be justified. Johnson & Johnson objected to the use of the claim which linked the attributes of speed and quality ie 'more nicotine faster.'; it was unclear as to what this 'more' nicotine, which was apparently being delivered faster, equated to.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare had stated that a pharmacokinetic study demonstrated that time to C_{max} (T_{max}) was significantly less for NiQuitin 21mg (6 hours) than Nicorette 25mg patch (12 hours), (p<0.0001). Data were also cited for C_{max}, which according to GlaxoSmithKline Consumer Healthcare, was 18.34ng/ml for NiQuitin and 16.56ng/ml for Nicorette (p=0.0021). However, Johnson & Johnson had been unable to verify these values as the data on file summary provided indicated that the C_{max} for NiQuitin Clear 21mg was 16.5ng/ml measured at 8 hours and 15.7ng/ml measured at 12 hours for the Nicorette 25mg patch.

Regardless of the actual data, C_{max} was a snapshot of the overall plasma profile and could not be used to justify a general claim that 'more nicotine' was delivered 'faster' than any other patch.

As regards the 'more' aspect of the claim, GlaxoSmithKline Consumer Healthcare argued that the $AUC_{0\text{-infinity}}$ for NiQuitin was higher than for Nicorette 25mg patch (382.4ng/ml*hr vs 243.7ng/ml*hr; p<0.0001). Johnson & Johnson did not disagree that the data presented appeared to support that the AUC was higher for NiQuitin but this did not mean that the amount delivered, as measured by the AUC, was delivered faster. The fact that T_{max} appeared to occur earlier with NiQuitin Clear 21mg compared with Nicorette 25mg patch could not justify that the total amount of nicotine delivered was delivered faster.

The Panel considered that the headline claim at issue would be read in conjunction with the prominent graph beneath. The graph compared the mean adjusted plasma nicotine concentrations of single dose NiQuitin 21mg patch with single dose Nicorette 25mg patch over 32 hours; the total area under the curve was greater for the NiQuitin patch which also reached its C_{max} (T_{max}) more rapidly (6 hours vs 12 hours; p<0.0001).

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that speed of delivery and AUC were related. Fant *el al* to which the claim was referenced was a pharmacokinetic crossover study to compare the absorption characteristics of three transdermal nicotine patches; a 15mg 16 hour patch, a 21mg 24 hour patch and NiQuitin 21mg 24 hour patch. The authors stated that the study demonstrated significant differences in nicotine delivery among transdermal patches at the highest marketed dose and approved duration of use. GlaxoSmithKline Consumer Healthcare did not refer to Fant *et al* in its response. Mention was made of Geiss *et al* dated 2010. The data on file to which both the claim at issue and graph were referenced was an open label study the primary objective of which was to demonstrate that NiQuitin 21mg patch was superior to Nicorette 25mg patch with respect to the $AUC_{0\text{-infinity}}$. One of the secondary objectives was to compare the products' single dose C_{max} and T_{max}. The study showed that, compared with the Nicorette 25mg patch, the NiQuitin 21mg patch had a statistically significantly higher $AUC_{0\text{-infinity}}$ (p<0.0001) and earlier T_{max} (6 hours vs 12 hours; p<0.0001). The NiQuitin 21mg patch also had a higher C_{max} (18.34ng/ml vs 16.56ng/ml).

Given the data set out above, the Panel did not consider that the claim 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch', in conjunction with the graph below, was ambiguous or misleading in relation to either C_{max} or AUC as alleged. Nor did the Panel consider that the claim in conjunction with the graph misleadingly implied higher nicotine levels for NiQuitin 21mg patch at each time point measured. The graph clearly showed that NiQuitin 21mg patch had higher nicotine concentrations at all time points other than at 12 and 14 hours when Nicorette 25mg patch had higher nicotine concentrations. The Panel considered that the claim was not misleading as alleged and thus ruled no breach of the Code.

Page 4 of the mailing (the centre inside page) headed 'Continuous daily use' featured a graph comparing plasma nicotine concentration (ng/ml) over time for NiQuitin 21mg patch, Nicorette 15mg patch and Nicotinell 21mg patch. The NiQuitin 21mg patch achieved higher peak plasma nicotine levels than either of the other two patches. The data shown was referenced to Fant *et al*.

Johnson & Johnson was concerned that the presentation of the data implied clinical superiority in terms of smoking cessation outcomes for the NiQuitin patch over other NRT patches, in particular the Nicorette 25mg patch.

Upon opening the leaflet the reader was presented with three consecutive pages comparing the NiQuitin 21mg patch with other NRT patches. The first page [considered above] displayed the single dose pharmacokinetic profiles for NiQuitin 21mg patch and Nicorette 25mg patch. The second of the three pages [ie the page now in question] presented a graph (adapted from Fant *et al*) showing the multiple dose pharmacokinetic profiles for three NRT patches. The third page included comparative efficacy claims relating to smoking cessation and compared NiQuitin 21mg patch with other NRT patches and Nicorette 25mg patch specifically.

Johnson & Johnson considered that the clear overall message of this three page spread was that the NiQuitin 21mg patch had a 'superior' single and multiple dose pharmacokinetic profile compared with other NRT patches and was therefore superior in terms of clinical efficacy. There was no evidence

to support this. Indeed, the 2008 Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation stated that 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

Johnson & Johnson noted that in Case AUTH/1253/11/01 the claim, 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette Patch', was alleged to be misleading as it linked pharmacokinetics to clinical efficacy. The claim was followed by a graph which was derived from Fant *et al*, used to support claims made in the current mailing. In its ruling, the Panel noted that the claim at issue was followed by a comparative efficacy discussion and in its opinion implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more smokers being able to successfully quit than with Nicorette. This was not known to be so and a breach of the Code was ruled.

Johnson & Johnson noted that in inter-company dialogue GlaxoSmithKline Consumer Healthcare did not deny that the mailing was presented in a way that could mislead the reader into believing that differences in pharmacokinetic profiles related to differences in smoking cessation outcomes. On the contrary, GlaxoSmithKline Consumer Healthcare had argued that based on the results of Tonnesen *et al* (1999), it had been established empirically and agreed conceptually that a product's pharmacokinetic profile was relevant to both symptom relief and cessation efficacy, and that it had been shown in a direct clinical comparison that NiQuitin 21mg patch achieved a significantly higher C_{max} and $AUC_{0\text{-}infinity}$, and a faster T_{max} than Nicorette 25mg.

Tonnesen *et al* was a double-blind, randomised, multicentre trial in 3,575 smokers to determine whether higher dosage and longer duration nicotine patch therapy increased success rates. The study demonstrated that 15mg and 25mg patches were superior to placebo and that the 25mg patch was superior to the 15mg patch. Tonnesen *et al* did not assess the efficacy of patches of any other strength, nor provide any comparative data with 24 hour patches. Furthermore, the study did not examine the pharmacokinetic profiles of the patches tested, nor whether these related in any way to efficacy.

In the absence of direct comparative clinical data, it could not be assumed that a higher level of nicotine delivery from a 24 hour patch compared with a 16 hour patch would result in improved efficacy. However, this was precisely what GlaxoSmithKline Consumer Healthcare seemed to suggest. It was possible that factors other than the actual amount of nicotine delivered could result in differences in clinical outcome eg it was yet to be established whether the break from nocturnal nicotine provided by the 16 hour patch was clinically beneficial.

Regardless of the above, there was no evidence to suggest that the different pharmacokinetic profiles observed with the 24 hour patch would result in improved clinical outcomes compared with any strength of 16 hour patch. Johnson & Johnson did not argue that pharmacokinetic profiles were not clinically relevant but simply that differences in pharmacokinetic profiles had not been proven to be of importance in terms of smoking cessation outcomes. Highlighting differences in pharmacokinetic profiles between patches, in the context of claims relating to the comparative efficacy, implied proven differences in terms of smoking cessation. This had not been proven to be the case.

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that its response on this point covered both the leaflet and covering letter. The Panel noted that whilst the leaflet might be read in light of the comments in the covering letter each had to be able to stand alone as regards the requirements of the Code. The Panel noted that Johnson & Johnson's allegations concerned the leaflet and were considered accordingly. The Panel noted that, nonetheless, some of its rulings might be relevant to the covering letter.

The Panel noted that when the leaflet was fully open three consecutive pages compared NiQuitin 21mg patch with other NRT patches. The left hand page featured the single dose pharmacokinetic data described above. The central page, headed 'Continuous daily use' featured a prominent graph comparing the plasma nicotine concentrations measured over 3 days' use of NiQuitin 21mg patch, Nicorette 15mg patch or Nicotinell 21mg patch. The claim 'By building on the previous 24 hours of delivery, NiQuitin 21mg Clear Patch delivers 30% higher blood levels of nicotine once steady state is reached, compared to day one' appeared above the graph. A claim beneath 'Smoking lapses are more likely to occur on the days morning cravings are elevated' was referenced to Shiffman *et al* (1997); it was then stated that 'NiQuitin 21mg 24-hour patch provides more effective protection against morning cravings and cravings throughout the day, than Nicorette 15mg 16-hour patch' referenced to Shiffman and Ferguson (2008). The next page was headed 'Proven short- and long-term quit rates' which compared the quit rate and efficacy of NiQuitin 21mg Patch with other NRT patches. With regard to quit rates this section claimed that no other patch had been shown to be more effective at 4 and 52 weeks including the Nicorette 25mg Invisipatch.

The Panel did not accept GlaxoSmithKline Consumer Healthcare's submission that the leaflet had three distinct sections none of which was a sub section to another. The design of the leaflet was such that the eye was naturally drawn from left to right across the three pages; from the pharmacokinetic data to the clinical claims regarding short- and long-term quit rates.

The Panel noted that Johnson & Johnson's complaint was that the leaflet presented pharmacokinetic data in such a way as to imply superiority in terms of smoking cessation outcomes for the NiQuitin 21mg patch over other NRT patches in particular the Nicorette 25mg patch. The complaint was not about differences in cigarette cravings or nicotine withdrawal symptoms.

The Panel noted that the three page spread of the leaflet presented, from left to right, single dose pharmacokinetic data (discussed above), multiple dose pharmacokinetic data (both of which implied advantages for NiQuitin 21mg patch) and then a page headed 'Proven short- and long-term quit rates'. In the Panel's view it was not unreasonable that readers might assume that the proven short- and long-term quit rates were as a direct consequence of the apparently favourable pharmacokinetic profiles depicted on the previous two pages. Given that the pharmacokinetic data implied advantages for the NiQuitin 21mg patch then it might be expected that the product produced better quit rates which was not so. Claims on the third page of the three-page spread noted and highlighted the percentage of short and long-term quitters on NiQuitin 21mg patch (~60% and ~20% respectively). In the Panel's view the use of highlighted figures implied an advantage for NiQuitin 21mg patch whereas it was possible that all NRT patches might result in quit rates of ~60% and ~20% at 4 and 52 weeks respectively. Indeed, under each of the claims it was stated that no other patch had been found to be more effective. In that regard the Panel noted that the Cochrane Review of 2008 had found no evidence of a difference in effect between 16 hour and 24 hour patches.

The Panel considered that whilst pharmacokinetic data was useful such data must not be presented in a way that implied consequential clinical benefits unless a direct link between the two had been established. The Panel considered that the leaflet was misleading as alleged on this point; it implied that the differences in pharmacokinetic profiles led to differences in quit rates and this had not been proven. A breach of the Code was ruled.

The Panel noted Johnson & Johnson's reference to Case AUTH/1253/11/01 and the claim 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette patch', referenced to Fant *et al*. In Case AUTH/1253/11/01 the Panel had noted that Fant *et al* was a pharmacokinetic study not an efficacy study. The claim at issue in that case followed a comparative efficacy discussion and, in the Panel's view, implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more smokers being able to successfully quit than with Nicorette. This was not known. The claim was considered misleading in this regard.

Turning to the present case the Panel noted that although there were some differences between Case AUTH/1253/11/01 and the leaflet presently at issue, both presented pharmacokinetic data from Fant *et al* including a graph depicting comparative nicotine concentrations. The Panel noted its ruling above of a breach in the present case as it had been implied that the differences in pharmacokinetic profiles resulted in differences in quit rates. In that regard the Panel thus considered that the leaflet in question was in breach of the undertaking given in Case AUTH/1253/11/01. A breach of the Code was ruled. High standards had not been maintained. A breach was ruled. Failure to comply with the undertaking in this instance brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The third page of the three-page inside spread was headed 'Proven short- and long-term quit rates' and featured two claims in highlighted boxes. The first claim read '~60% of abrupt quitters remain quit at 4 weeks with NiQuitin 21mg Clear Patch' referenced to the Transdermal Nicotine Study Group (TNSG) (1991) and Shiffman *et al* (2002).

Johnson & Johnson noted that the TNSG publication reported the results from two multicentre, clinical trials using 21, 14 or 7mg patches over 24 hours. The two studies were randomised, double-blind, placebo-controlled, parallel group trials of 6 weeks' duration and included 935 patients. Successful abstainers were then entered into a third trial for weaning (6 weeks) and off-drug follow up (12 weeks). Short-term abstinence rates for the two trials were measured as smoking cessation during the last 4 weeks of the 6 week full dose period. Abstinence at 6 weeks was 61%, 48%, and 27% for the 21mg, 14mg and placebo patches respectively. The main outcome measure repeatedly referred to in the paper was 4 weeks of continuous abstinence measured at 6 weeks, not smoking cessation measured at 4 weeks.

Shiffman *et al* (2002) reported data from two studies. The first was the TNSG study referred to above and the second was a study comparing nicotine lozenge with placebo. As already stated, the main outcome measure for the TNSG study was abstinence at 6 weeks.

GlaxoSmithKline Consumer Healthcare confirmed that the outcome measure for the TNSG study was 4 weeks' continuous abstinence measured at 6 weeks. Johnson & Johnson thus alleged that the claim that '~60% of abrupt quitters remain quit at 4 weeks with NiQuitin 21mg Clear Patch' was inaccurate and misleading.

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that readers would be familiar with 4 week quit rates as they were a routine NHS measurement and referred to 4 week quit rates, carbon monoxide (CO) verified continuous abstinence measured at 6 weeks. The Panel noted that the abstinence rates in the TNSG study were CO verified; 61% of subjects were continuously abstinent at the end of 6 weeks;

p≤0.001 vs placebo. The Panel noted that the claim at issue read '~60 of abrupt quitters *remain* quit at 4 weeks …' (emphasis added). The Panel considered that it was thus sufficiently clear that the claim referred to continuous abstinence. The Panel did not consider it misleading to not state that the 4 week data was measured at the 6 week time point. Readers would be familiar with how 4 week quit data was measured. The Panel did not consider that the claim was misleading as alleged; no breach of the Code was ruled.

The claim 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch' appeared beneath the claim at issue above within the same highlighted box. Johnson & Johnson stated that the claim at issue was a top parity claim which it understood meant under the Code that there were direct comparative data and hence the NiQuitin 21mg patch had been shown to be at least as effective as other available patches in head-to-head comparisons. This was not so.

Johnson & Johnson noted that GlaxoSmithKline Consumer Healthcare believed that the Code did not require the claim to be supported with direct head-to-head comparisons. However in Case AUTH/1402/12/02, GlaxoSmithKline Consumer Healthcare complained about a very similar claim for Nicorette Patch ie 'No other patch is proven more effective at beating cigarettes' and alleged that '…top parity claims could not be made without head-to-head comparisons with all other patches, which had not been done'. The Panel ruled that the claim implied Nicorette Patch was the most effective patch at beating cigarettes and ruled a breach of the Code. Johnson & Johnson therefore alleged that the claim now at issue was in breach of the Code.

The Panel noted that whilst top parity claims were not prohibited under the Code care should be taken to ensure that they did not give a misleading impression of a product's relative efficacy, were capable of substantiation and otherwise complied with the Code. Every case had to be considered on its own merits. The context in which a claim appeared was important.

The Panel noted that both parties referred to Case AUTH/1402/12/02 wherein the claims 'No other patch offers smokers a greater chance of success', 'No other patch is proven more effective at beating cigarettes' and 'No other nicotine patch works harder at beating cigarettes …' were ruled in breach. The Panel had noted that there was no comparative data on all the available nicotine patches. The claims implied that Nicorette patch was the most effective patch at beating cigarettes. No material or comment in relation to substantiation of the claims was provided. On the data before it the Panel considered that the claims were not capable of substantiation.

Turning back to the case now before it, Case AUTH/2298/2/10, the Panel noted GlaxoSmithKline Consumer Healthcare's submission that there was no evidence to suggest that other nicotine patches were any more effective than NiQuitin patches as assessed by 4 week quit rates. The Panel, however, noted the company's subsequent submission that it was not aware of any data on 4 week quit rates for Nicotinell 21mg patches. In that regard the Panel considered the claim 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch' was misleading. Further, context was important. The Panel considered that the comparative theme of the leaflet meant that the claim at issue was likely to be read as a superiority claim and was thus misleading in this regard. Breaches of the Code were ruled.

The second highlighted box on the third page of the centre of the leavepiece featured the claim: '~ 20% of quitters remain quit at 52 weeks with NiQuitin 21mg Clear Patch' referenced to Aubin *et al* (2008). Johnson & Johnson noted that it was not stated that Aubin *et al* was an open-label study which was a critical piece of information that the reader should know. In Case AUTH/2203/1/09, the Panel stated regarding this study; '… whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data.'

In inter-company dialogue GlaxoSmithKline Consumer Healthcare argued that Aubin *et al* was presented as one example, not the data set in its entirety which was why the open-label design did not need to be stated. Johnson & Johnson disagreed. No other supporting reference was given and the reader had not been provided with all the necessary information to assess the claim based on the single reference provided.

The Panel noted each party's submission about Aubin *et al* and Case AUTH/2203/1/09 wherein Aubin *et al* was the sole data set to support a superiority claim for varenicline vs NRT. The Panel considered that the present case was different. Aubin *et al* was being used for its NRT results and there was other data including Richmond *et al*, a randomised, placebo-controlled trial, to the support claim at issue. The Panel considered that the claim '~20% of quitters remain quit at 52 weeks with NiQuitin 21mg Clear Patch' was not misleading as alleged. No breach of the Code was ruled.

The claim 'No other patch has been shown to be more effective at 52 weeks, including Nicorette 25mg Invisipatch' appeared beneath the claim considered above within the same highlighted box. For the same reasons described above, Johnson & Johnson alleged that the claim implied superiority for the NiQuitin 21mg patch over other patches. As already stated, there were no head-to-head studies showing that the NiQuitin 21mg patch was more effective than marketed patches. For the reasons outlined above breaches of the Code were alleged.

The Panel noted that the Cochrane Review 2008 stated 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'. The Panel considered its comments above about context and the comparative theme of the leaflet were nonetheless relevant. The Panel considered that given the comparative nature of the leaflet the claim was likely to be read as a superiority claim and was thus misleading in this regard. Breaches of the Code were ruled.

The covering letter was headed 'Which therapeutic nicotine patch delivers more nicotine faster than any other patch?' and began by discussing the pharmacokinetic data at issue above. Subsequent paragraphs discussed morning cravings and general effectiveness.

Johnson & Johnson referred to the claim 'Reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch' which appeared as the first of two bullet points near the start of the letter. Although the graph within the leaflet appeared to support this claim, as discussed above, Johnson & Johnson had been unable to verify the values given by GlaxoSmithKline Consumer Healthcare for the comparative C_{max} values and it had not been made clear whether these differences were statistically significant. Irrespective of statistical significance, C_{max} was of minimal clinical relevance for nicotine patches which were designed to deliver steady levels of nicotine over a prolonged period of time. Inclusion of this claim, particularly in such a prominent position in the letter, implied that this data was relevant to the clinical scenario and the decision to prescribe NiQuitin 21mg patch rather than Nicorette 25mg Invisipatch.

In inter-company dialogue, GlaxoSmithKline Consumer Healthcare stated that it believed that the delivery characteristics of the patch were fundamental to its clinical success. However, as already stated, Johnson & Johnson was not aware of any data to suggest that the NiQuitin 21mg patch was superior in terms of clinical success compared with Nicorette 25mg patch. There were no data whatsoever to suggest that time to peak plasma concentration was relevant to the choice of which patch to prescribe. Peak plasma level was given undue prominence in the letter suggesting that it was clinically important. This was not so. Johnson & Johnson thus believed that the claim was misleading.

The Panel considered its comments above about the pharmacokinetic data and clinical outcome were relevant; the consequential link between the pharmacokinetic data and the clinical claims had not been established. A reader would not unreasonably assume that the favourable pharmacokinetic data led to the favourable clinical data discussed subsequently in the letter; effective relief from morning cravings and effectiveness at 4 and 52 weeks. The causal link had not been established and the claim was misleading in this regard. A breach of the Code was ruled.

The letter contained the following paragraph: '16-hour patch wear means that blood nicotine concentrations drop to minimal levels overnight when the patch is removed and may be why NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15mg 16-hour patches. Even though most lapses happen later in the day, they are more likely to occur on the days when morning cravings are elevated'.

Johnson & Johnson believed that the suggestion that nocturnal nicotine dosing with the 24-hour patch '…may be why NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15 mg 16-hour patches' was speculation. Johnson & Johnson was not aware of any robust data demonstrating that wearing a patch overnight was related to improved cravings scores throughout the day. There could be a number of reasons to explain differences between the 21mg 24 hour patch and 15mg 16 hour patch in cravings relief including difference in overall strength between the two.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare cited the NiQuitin 21mg patch SPC which stated: 'Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings'. This statement related to morning cravings. It did not support the claim at issue which suggested that nocturnal nicotine dosing might provide more effective protection against cravings throughout the day.

The Panel noted GlaxoSmithKline Consumer Healthcare's submissions that the claim at issue was written as postulation, and did not state that 24-hour patch wear was the only possible explanation, and that Johnson & Johnson had not provided any data to refute the suggestion that nocturnal dosing might be related to an improvement in cravings throughout the day. The Panel noted that claims had to be capable of substantiation.

The Panel noted that the NiQuitin 21mg patch SPC stated that use for 24 hours was recommended to optimise effect against morning cravings. The claim at issue related to 'protection against cravings throughout the day'. The Panel noted that the only data showing improved craving control throughout the day for the 24-hour patch was for heavily dependent smokers rather than the general smoking population (Shiffman *et al* 2000). The Panel considered that the phrase 'may be' was insufficient to negate the impression that nocturnal nicotine dosing did provide more effective protection against cravings throughout the day in the general smoking population. This impression was compounded by the subsequent paragraph which referred to optimizing protection against morning cravings (in

line with the SPC) and providing a level of nicotine in the blood stream on waking that could be built on with the application of the next patch. A subsequent claim referred to NiQuitin 21mg patch's general effectiveness compared to other patches. The Panel considered the claim at issue misleading as alleged. A breach of the Code was ruled.

Johnson & Johnson was concerned that the paragraph referred to above represented breaches of the Code including a breach of a previous undertaking. The first claim '… NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15mg 16-hour patches' was referenced to Shiffman *et al* (1997) (reference 3). The second claim 'Even though most lapses happen later in the day, they are more likely to occur on the days when morning cravings are elevated' was referenced to Shiffman and Ferguson (2008) (reference 4).

Shiffman *et al* (1997) was a non-comparative study which assessed urge and lapse in smokers who had recently quit. It did not demonstrate that the NiQuitin 21mg patch provided more effective protection against cravings than the Nicorette patch. GlaxoSmithKline Consumer Healthcare had acknowledged that the referencing was wrong and agreed to correct this in future iterations. Johnson & Johnson assumed that references 3 and 4 had been mixed up.

Shiffman and Ferguson was an analysis of two randomised clinical studies. The first study cited compared a 21mg 24 hour patch with a placebo patch (n=102) while the second study compared a 21mg 24 hour patch with a 15mg 16 hour patch (n=244). Overall the authors concluded that the first study showed that the 21mg patch was effective in reducing cravings throughout the day compared with placebo and that the second study showed that cravings were lower at all times during the day with the 21mg patch compared with the 15mg patch.

Johnson & Johnson noted that in Case AUTH/1401/12/02 the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' was ruled in breach of the Code. It was alleged that the claim contributed to the overall impression that 24 hour patches had greater efficacy in achieving smoking cessation than 16 hour patches. There were no data available at the time to show clinical differences between 16 and 24 hour patches and this situation had not changed. Indeed, the 2008 Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation stated that 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

In the letter now at issue, Johnson & Johnson believed that the reader would assume that the stated reduction in cravings throughout the day apparently achieved with 24-hour patches was such that NiQuitin 21mg patch had greater efficacy in achieving smoking cessation compared with the 16 hour patch. This was compounded by the link to lapses in the proceeding claim.

Moreover, Shiffman *et al* (1997), which Johnson & Johnson believed was the reference GlaxoSmithKline Consumer Healthcare intended to use to support the claim that morning cravings and lapses were linked (this was the case for the accompanying leaflet), was conducted in smokers who had recently quit and were not using pharmacotherapy to treat their nicotine withdrawal. There was no evidence to suggest that the pattern of cravings and lapses was the same as for the patients being treated with NRT. Therefore, for all the reasons cited, Johnson & Johnson believed that these claims were in breach. It also believed that the implication that improvements in cravings relief were associated with higher smoking cessation outcomes was a breach of undertaking.

The Panel noted Johnson & Johnson's allegation that there was no evidence to suggest that the pattern of cravings and lapses in Shiffman *et al* (1997) applied to patients being treated with NRT. The Panel did not accept that Figure 1 in Shiffman and Ferguson provided *prima facie* support as suggested by GlaxoSmithKline Consumer Healthcare; it depicted placebo-controlled data. The study authors noted that smoking lapses commonly occurred in the evening and late night hours but the authors did not observe higher craving during these time periods. The authors noted that many studies had shown that smoking lapses were associated with acute increases in craving when smokers experienced provocative situations and thus the occurrence of such lapses during the evening and night hours might be due to exposure to such stimuli rather than to any inherent diurnal rhythm in the intensity of background craving. The Panel considered the claim was misleading as alleged. A breach of the Code was ruled.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that in Case AUTH/1401/12/02 it was alleged that the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' inferred a greater likelihood of success in smoking cessation with a 24-hour patch than with a 16-hour patch. The Appeal Board, *inter alia*, considered that the claim implied that because NiQuitin CQ was effective in relieving morning cravings, it would also be effective in long-term smoking cessation. The phrase 'from the word go' appeared to differentiate NiQuitin CQ from the 16-hour patches referred to in

the preceding paragraph. The Appeal Board considered that the claim implied that NiQuitin CQ 24-hour patch was more likely to help a patient to stop smoking than a 16-hour patch. The Appeal Board considered that the claim overstated the data and was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Turning to the present case, Case AUTH/2298/2/10, the Panel noted that there were some differences between the paragraph at issue and the claim considered previously. Nonetheless, the Panel considered that the claims at issue implied that as lapses were more likely to occur when morning cravings were elevated, the more effective protection against cravings afforded by the 24-hour patch meant that NiQuitin 21mg patch was more likely to help a patient stop smoking than a 16-hour patch. There was no evidence this was so. This impression was misleading, a breach of Clause 7.2 was ruled. Further this impression was contrary to the undertaking given in Case AUTH/1401/12/02 and thus a breach of the Code was ruled. High standards had not been maintained. A breach was ruled. Failure to comply with the undertaking in this instance bought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Johnson & Johnson noted that the claim 'No other patch is proven more effective than NiQuitin 21mg Clear Patch at 4 or 52 weeks' in the letter was very similar to the claims about short- and long-term quit rates in the leaflet. Johnson & Johnson alleged, as described above, that the claim implied superiority in terms of cessation rates for the NiQuitin 21mg patch over other patches. This was not so and thus Johnson & Johnson believed that this claim was in breach of the Code.

The Panel considered that rulings above were relevant here. Breaches of the Code were ruled.

Johnson & Johnson Limited complained about the promotion of NiQuitin 21mg Clear Patch (nicotine replacement therapy (NRT)) by GlaxoSmithKline Consumer Healthcare. The material at issue was a mailing which comprised a leaflet and a covering letter, each bore the reference NCQ/SYN/KG/1109/01. The date of preparation for both items was December 2009. Inter-company dialogue had failed to resolve all of the issues. NiQuitin Clear was indicated for the relief of nicotine withdrawal symptoms including cravings as an aid to smoking cessation.

As possible breaches of the undertakings given in Cases AUTH/1253/11/01 and AUTH/1401/12/02 were alleged, that part of the case was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings. The Authority thus asked GlaxoSmithKline Consumer Healthcare to comment in relation to Clauses 2 and 9.1 of the Code as well as Clause 25 referred to by Johnson & Johnson.

A Leaflet

The six page, gate folded leaflet was entitled 'Which therapeutic nicotine patch delivers more nicotine faster than any other patch?' A diagonal flash on the front page referred to 'New data'.

1 Claim 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch'

Page 2 of the leaflet was headed 'From day one' followed by the remainder of the claim at issue which was referenced to Fant *et al* (2000) and data on file. Beneath, a graph showed comparative mean adjusted plasma nicotine concentrations from a single dose of NiQuitin 21mg patch or Nicorette 25mg patch over 32 hours. Data for the graph came from the data on file.

COMPLAINT

Johnson & Johnson alleged that the claim was ambiguous and as such misleading, in breach of Clause 7.2. The ambiguity was primarily due to lack of clarity relating to the measures of speed and extent of nicotine delivery upon which the claim was based. The reference to 'more' nicotine being delivered 'faster' with NiQuitin than with other patches could relate to a number of measures:

- Higher and more rapid peak plasma level (C_{max})
- Higher and more rapid total nicotine delivery (area under the curve (AUC))
- Higher nicotine levels at every timepoint measured.

The data presented appeared to show that the (C_{max}) was higher and achieved more rapidly with the NiQuitin patch. However, it was not clear from the page whether the difference was statistically significant. Irrespective of the statistical significance, C_{max} was of little clinical relevance for nicotine patches which were designed to deliver sustained, steady plasma levels over an extended period. It might be that the data presented indicated that C_{max} was achieved more rapidly with the NiQuitin 21mg patch, but this was not the same as delivering 'more nicotine faster…'. C_{max} was not a measure of the amount of nicotine delivered but merely a snap shot of plasma levels at one time point.

The Nicorette 16 hour patch was intended to be removed after 16 hours and so it delivered its nicotine dose faster than the NiQuitin 21mg patch which was intended to be removed 24 hours after application. Indeed, the NiQuitin patch would continue to deliver nicotine for eight hours after the Nicorette patch had been removed. The 'full therapeutic dose' of nicotine was therefore delivered considerably quicker with the Nicorette patch than with the NiQuitin patch.

In inter-company dialogue GlaxoSmithKline

Consumer Healthcare had noted that NiQuitin Clear 21mg patch could be worn for 16 or 24 hours. Johnson & Johnson submitted that this might be true but the NiQuitin patch was clearly intended to be used for 24 hours; the summary of product characteristics (SPC) stated: 'NiQuitin Clear patches should be applied once a day, at the same time each day and preferably soon after waking, to a non-hairy, clean, dry skin site and worn continuously for 24 hours. The NiQuitin Clear patch should be applied promptly on removal from its protective sachet. Patches may be removed before going to bed if desired. However, use for 24 hours is recommended to optimise the effects against morning cravings'.

The vast majority of clinical evidence for the NiQuitin patch was from clinical studies of 24 hour usage.

As regards the AUC, this was a measure of the total amount of nicotine delivered. Therefore, Johnson & Johnson believed that this measure was of particular relevance in the context of the claim that 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch'.

In the context of a patch applied daily, the claim 'delivers more nicotine faster' could only reasonably be assumed to refer to the total delivery of nicotine as measured by AUC. Given that AUCs for the two patches would always be measured or calculated over a specific period (eg $AUC_{0\text{-}24}$) and that for the comparison to be fair, this time should be the same for both patches. One patch clearly could not deliver its measured AUC faster than another patch. Comparative AUCs could be higher but not faster.

Another possible interpretation of the claim was that NiQuitin 21mg Clear patch delivered a higher level of nicotine at each time point. This was not the case as levels were higher for the Nicorette 25mg patch at 12 and 14 hours.

Johnson & Johnson noted that GlaxoSmithKline Consumer Healthcare justified 'faster' and 'more' independently of each other. Even if these two individual statements were true, this did not mean that the overall claim which linked the amount of nicotine delivered and speed of delivery could be justified. Johnson & Johnson objected to the use of the claim which linked the attributes of speed and quality ie 'more nicotine faster.'; it was unclear as to what this 'more' nicotine, which was apparently being delivered faster, equated to.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare had stated that a pharmacokinetic study demonstrated that time to C_{max} (T_{max}) was significantly less for NiQuitin 21mg (6 hours) than Nicorette 25mg patch (12 hours) ($p<0.0001$). Data were also cited for C_{max}, which according to GlaxoSmithKline Consumer Healthcare, was 18.34ng/ml for NiQuitin and 16.56ng/ml for Nicorette ($p=0.0021$). However, Johnson & Johnson had been unable to verify these values as the data on file summary provided indicated that the C_{max} for NiQuitin Clear 21mg was 16.5ng/ml measured at 8 hours and 15.7ng/ml measured at 12 hours for the Nicorette 25mg patch.

Regardless of the actual data, C_{max} was simply a snapshot of the overall plasma profile and could not be used to justify a general claim that 'more nicotine' was delivered 'faster' than any other patch.

As regards the 'more' aspect of the claim, GlaxoSmithKline Consumer Healthcare argued that the $AUC_{0\text{-}infinity}$ for NiQuitin was higher than for Nicorette 25mg patch (382.4ng/ml*hr vs 243.7ng/ml*hr; $p<0.0001$). Johnson & Johnson did not disagree that the data presented appeared to support that the AUC was higher for NiQuitin but this did not mean that the amount delivered, as measured by the AUC, was delivered faster. The fact that T_{max} appeared to occur earlier with NiQuitin Clear 21mg compared with Nicorette 25mg patch could not justify that the total amount of nicotine delivered was delivered faster.

Johnson & Johnson alleged that the claim was ambiguous and misleading in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson initially believed that the ambiguity of the claim at issue was primarily due to lack of clarity relating to the measures of speed and extent of nicotine delivery upon which the claim was based. The company then listed three possible interpretations;

- Higher and more rapid C_{max}

The data supported this interpretation. C_{max} was significantly higher with the NiQuitin 21mg patch ($p=0.0031$) and time to reach the peak concentration was significantly faster with the NiQuitin 21mg patch ($p<0.0001$) (Geiss *et al* 2010).

- Higher and more rapid total nicotine delivery.

The data on file supported this interpretation. The primary endpoint of the study was $AUC_{0\text{-}infinity}$ and this was shown to be statistically significantly higher with NiQuitin 21mg patch ($p<0.0001$).

- Higher nicotine levels at every time point measured.

The claim did not state 'delivers more nicotine at each time point'; it stated that the NiQuitin 21mg patch delivered more nicotine faster. The clear and simple graphics were unambiguous and displayed the time points where NiQuitin 21mg patch levels were numerically lower than the comparator with clear white space between the lines, ensuring that even a casual reader would not believe that NiQuitin 21mg patch had higher nicotine levels at each individual time point.

It was clear from the slope of the graphs from the head-to-head studies in the leaflet that NiQuitin 21mg patch delivered nicotine more rapidly than other patches. It was also clear (and Johnson & Johnson agreed), that it delivered more nicotine to the patient than the Nicorette 25mg patch as the $AUC_{0\text{-infinity}}$ was higher ($p<0.0001$). The initial rapid rise in nicotine levels were then maintained and contributed to a higher AUC. The shape of the graphs themselves determined the area underneath them, and therefore the amount of nicotine that the individual was exposed to in a given time. Thus the two features of speed of delivery and AUC were related.

GlaxoSmithKline Consumer Healthcare submitted that Johnson & Johnson had confused the issue by asserting that because Nicorette was only worn for 16 hours, it delivered its 'full therapeutic dose' faster. This was not relevant because Nicorette 16 hour patches continued to deliver about 20% of their dose after removal of the patch due to absorption of nicotine from the skin depot (Benowitz *et al* 1992, Johansson *et al* 1996). Thus although only worn for 16 hours, part of the 'full therapeutic dose' continued to be delivered after its removal. Also the SPC for NiQuitin 21mg patch made it clear that it was also able to be used as a 16 hour patch if desired. There were no caveats in the SPC regarding 16 or 24 hour wear apart from the desire to do so. However, the SPC highlighted that 24 hour wear optimised the effect against morning cravings as it was important for prescribers and users to understand the risks and benefits of 24 hour and 16 hour wear and this was recognised by the licensing authority. C_{max}, $AUC_{0\text{-}16}$, and $AUC_{0\text{-infinity}}$ assuming a 16 hour application of the 21mg patch were also significantly higher, (Geiss *et al*) so the claim in question still held true whether NiQuitin 21mg patch was worn for 16 or 24 hours.

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson further stated that in the context of a patch applied daily, the claim 'delivers more nicotine faster' could only reasonably be assumed to refer to the total delivery of nicotine as measured by AUC and that for the comparison to be fair, this time should be the same for both patches. GlaxoSmithKline Consumer Healthcare agreed with this interpretation and was confused as Johnson & Johnson appeared to contradict its initial assertion that the claim was ambiguous. GlaxoSmithKline Consumer Healthcare agreed that AUC had to be assessed over the same time period for both patches and it was. Although duration of patch wear was different between the patches, the calculations were based on the same time period over all. The primary end point was $AUC_{0\text{-infinity}}$ and this was statistically significantly higher for NiQuitin 21mg ($p<0.0001$). It was also significantly higher in a post hoc analysis of $AUC_{0\text{-}16}$ and $AUC_{0\text{-infinity}}$ assuming a 16 hour application of the 21mg patch (Geiss *et al*).

NiQuitin's AUC was bigger than Nicorette's AUC over the same time period. If more nicotine was delivered per unit time then this was the definition of rate and thus faster. No claims were made for specific C_{max} levels in any materials, but simply that NiQuitin 21mg patch 'reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch', which was supported by the comparative T_{max} data (6 vs 12 hours; $p<0.0001$) (Geiss *et al*). GlaxoSmithKline Consumer Healthcare explained that the apparent discrepancy in the values in the data on file table and the actual C_{max} values calculated in the study was because the nicotine concentrations cited in the data on file table were the mean nicotine levels at each time point whereas the C_{max} in the study synopsis was the mean of each individual's C_{max}.

The claim was substantiated by the data which Johnson & Johnson agreed showed that NiQuitin 21mg patch delivered more nicotine (greater AUC) faster (more rapid rise of nicotine levels, earlier T_{max}). Delivery of drug per unit time was the rate of delivery. NiQuitin 21mg patch delivered more nicotine per unit time, thus supporting the claim that it delivered more nicotine faster. The data showed it also had a higher C_{max} than Nicorette 25mg although no claims were made in this regard.

Thus GlaxoSmithKline Consumer Healthcare refuted the allegation that the claim was ambiguous and misleading, in breach of Clause 7.2.

PANEL RULING

The Panel considered that the headline claim at issue would be read in conjunction with the prominent graph beneath. The graph compared the mean adjusted plasma nicotine concentrations of single dose NiQuitin 21mg patch with single dose Nicorette 25mg patch over 32 hours; the total area under the curve was greater for the NiQuitin patch which also reached its C_{max} (T_{max}) more rapidly (6 hours vs 12 hours; $p<0.0001$).

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that speed of delivery and AUC were related. Fant *el al* to which the claim at issue was referenced was a pharmacokinetic crossover study to compare the absorption characteristics of three transdermal nicotine patches; a 15mg 16 hour patch, a 21mg 24 hour patch and NiQuitin 21mg 24 hour patch. The authors stated that the study demonstrated significant differences in nicotine delivery among transdermal patches at the highest marketed dose and approved duration of use. GlaxoSmithKline Consumer Healthcare did not refer to Fant *et al* in its response. Mention was made of Geiss *et al* dated 2010. The data on file to which both the claim at issue and graph were referenced was an open label study the primary objective of which was to demonstrate that NiQuitin 21mg patch was superior to Nicorette 25mg patch with respect to the $AUC_{0\text{-infinity}}$. One of the secondary objectives was to compare the products' single dose C_{max} and T_{max}. The study showed that, compared with the Nicorette 25mg patch, the NiQuitin 21mg patch had a statistically significantly higher $AUC_{0\text{-infinity}}$

($p<0.0001$) and earlier T_{max} (6 hours vs 12 hours; $p<0.0001$). The NiQuitin 21mg patch also had a higher C_{max} (18.34ng/ml vs 16.56ng/ml).

Given the data set out above, the Panel did not consider that the claim 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch', in conjunction with the graph below, was ambiguous or misleading in relation to either C_{max} or AUC as alleged. Nor did the Panel consider that the claim at issue in conjunction with the graph misleadingly implied higher nicotine levels for NiQuitin 21mg patch at each time point measured. The accompanying graph clearly showed that NiQuitin 21mg patch had higher nicotine concentrations at all time points other than at 12 and 14 hours when Nicorette 25mg patch had higher nicotine concentrations. The Panel considered that the claim was not misleading as alleged and thus ruled no breach of Clause 7.2.

2 Implied improvements in efficacy based on pharmacokinetic data

Page 4 of the mailing (the centre inside page) headed 'Continuous daily use' featured a graph comparing plasma nicotine concentration (ng/ml) over time for NiQuitin 21mg patch, Nicorette 15mg patch and Nicotinell 21mg patch. The NiQuitin 21mg patch achieved higher peak plasma nicotine levels than either of the other two patches. The data shown was referenced to Fant *et al*.

COMPLAINT

Johnson & Johnson was concerned that the presentation of the data implied clinical superiority in terms of smoking cessation outcomes for the NiQuitin patch over other NRT patches, in particular the Nicorette 25mg patch.

Upon opening the leaflet the reader was presented with three consecutive pages comparing the NiQuitin 21mg patch with other NRT patches. The first page [considered in Point A1 above] displayed the single dose pharmacokinetic profiles for NiQuitin 21mg patch and Nicorette 25mg patch. The second of the three pages [ie the page now in question] presented a graph (adapted from Fant *et al*) showing the multiple dose pharmacokinetic profiles for three NRT patches. The third page included comparative efficacy claims relating to smoking cessation and compared NiQuitin 21mg patch with other NRT patches and Nicorette 25mg patch specifically.

Johnson & Johnson considered that the clear overall message of this three page spread was that the NiQuitin 21mg patch had a 'superior' single and multiple dose pharmacokinetic profile compared with other NRT patches and was therefore superior in terms of clinical efficacy. There was no evidence to support this. Indeed, the 2008 Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation stated that 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

Johnson & Johnson believed that there were parallels to be drawn with Case AUTH/1253/11/01 in which it was alleged that the claim 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette Patch' was misleading as it linked pharmacokinetics to clinical efficacy. The claim was followed by a graph which was derived from Fant *et al*, used to support claims made in the current mailing. In its ruling, the Panel noted that the claim at issue was followed by a comparative efficacy discussion and in its opinion implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more smokers being able to successfully quit than with Nicorette. This was not known to be so and a breach of the Code was ruled.

Johnson & Johnson noted that in inter-company dialogue GlaxoSmithKline Consumer Healthcare did not deny that the mailing was presented in a way that could mislead the reader into believing that differences in pharmacokinetic profiles related to differences in smoking cessation outcomes. On the contrary, GlaxoSmithKline Consumer Healthcare had argued that based on the results of Tonnesen *et al* (1999), it had been established empirically and agreed conceptually that a product's pharmacokinetic profile was relevant to both symptom relief and cessation efficacy, and that it had been shown in a direct clinical comparison that NiQuitin 21mg patch achieved a significantly higher C_{max} and $AUC_{0\text{-infinity}}$, and a faster T_{max} than Nicorette 25mg.

Tonnesen *et al* was a double-blind, randomised, multicentre trial in 3,575 smokers to determine whether higher dosage and longer duration nicotine patch therapy increased success rates. The study compared 15mg and 25mg 16 hour patches with placebo and demonstrated that both patches were superior to placebo and that the 25mg patch was superior to the 15mg patch. Tonnesen *et al* did not assess the efficacy of patches of any other strength, nor provide any comparative data with 24 hour patches. Furthermore, the study did not provide any information relating to the pharmacokinetic profiles of the patches tested, nor whether these related in any way to efficacy.

In the absence of direct comparative clinical data, it could not be assumed that a higher level of nicotine delivery from a 24 hour patch compared with a 16 hour patch would result in improved efficacy. However, this was precisely what GlaxoSmithKline Consumer Healthcare seemed to suggest. It was possible that factors other than the actual amount of nicotine delivered could result in differences in clinical outcome. For instance it was yet to be established whether the break from nocturnal nicotine provided by the 16 hour patch could result in a clinical benefit.

Regardless of the above, there was no evidence to suggest that the different pharmacokinetic profiles observed with the 24 hour patch would result in improved clinical outcomes compared with any strength of 16 hour patch. Johnson & Johnson did not argue that pharmacokinetic profiles were not clinically relevant as suggested by GlaxoSmithKline Consumer Healthcare, but simply that differences in pharmacokinetic profiles had not been proven to be of importance in terms of smoking cessation outcomes for nicotine patches.

Highlighting differences in pharmacokinetic profiles between patches, in the context of claims relating to the comparative efficacy, implied proven differences in terms of smoking cessation. This had not been proven to be the case. Therefore, Johnson & Johnson alleged a breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson had alleged that the comparative pharmacokinetic data depicted graphically implied clinical superiority with regard to smoking cessation outcomes; it believed there were parallels to be drawn from Case AUTH/1253/11/01.

The undertaking given by GlaxoSmithKline Consumer Healthcare in relation to the ruling of a breach of Clause 7.2 in Case AUTH/1253/11/01 was to more clearly link the clinical relevance of comparative pharmacokinetic profiles to relief of craving rather than directly following discussion of long-term successful quitting compared with placebo. The leaflet and letter now at issue were sufficiently different so that they did not breach this previous undertaking. The leaflet and the letter were provided as one item and as such GlaxoSmithKline Consumer Healthcare had considered them together as similar allegations were made by Johnson & Johnson in relation to the letter.

The letter discussed the new pharmacokinetic data for NiQuitin 21mg/24hr compared with Nicorette 25mg/16hr patches, followed by a comparison of craving relief (not quit rates) between NiQuitin 21mg/24hr and Nicorette 15mg/16hr in a separate paragraph. This was then followed by the relief of morning cravings by 24 hour wear of NiQuitin 21mg/24hr patch, and that was followed by a sentence on quit rates that specifically did not state that rates were higher with NiQuitin 21mg Clear patch. The headline and highlighted take out message from the letter was that NiQuitin 21mg Clear patch delivered more nicotine than other patches, not that it had higher quit rates. The reader was then referred to the enclosed leaflet for further information on the new data, below which was the headline claim for that study.

The leaflet had three distinct sections, the first of which discussed the new pharmacokinetic data for NiQuitin 21mg/24hr compared with Nicorette 25mg/16hr patches, the second compared pharmacokinetic profiles for three NRT patches and compared craving relief (not quit rates) between NiQuitin 21mg/24hr and Nicorette 15mg/16hr patches, the third discussed short- and long-term quit rates. None of the three sections was a sub section to another.

Johnson & Johnson alleged that the overall message of the three page spread was that the NiQuitin 21mg patch had a superior pharmacokinetic profile and therefore had superior clinical efficacy. Johnson & Johnson stated that it did not argue that pharmacokinetic profiles were not clinically relevant…but simply that differences in pharmacokinetic profiles had not been proven to be of importance in terms of smoking cessation outcomes for nicotine patches. Throughout its complaint Johnson & Johnson consistently assumed that smoking cessation was the only point of clinical relevance for health professionals and therefore any data provided would be interpreted in the context of long-term quit rates. Also, its interpretation of 'clinical efficacy' related solely to smoking cessation. In addition to that quoted above, GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson quoted the following from the 2008 Cochrane Review, 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch:..'. Johnson & Johnson had also stated that there was no evidence to suggest that the different pharmacokinetic profiles observed with the 24 hour patch would result in improved clinical outcomes compared with any strength of 16 hour patch. The same assumptions and interpretation were also evident in Johnson & Johnson's comments regarding GlaxoSmithKline Consumer Healthcare's discussion of Tonnesen *et al*, the quotations from which had been picked and presented in such a way that their meaning had been altered (further comment on Tonnesen *et al* was made below).

Clinical efficacy is not just quit rates

GlaxoSmithKline Consumer Healthcare noted that NiQuitin 21mg patches were indicated for 'the relief of nicotine withdrawal symptoms including cravings as an aid to smoking cessation'. Thus 'clinical efficacy' referred not just to smoking cessation but also craving relief. It was therefore appropriate to discuss both in promotional materials. Efficacy in the reduction of cravings and withdrawal symptoms had long been recognised as an important clinical endpoint as evidenced by the licensed indications of both oral and transdermal NRT products. Furthermore in the eight years since the rulings made in Case AUTH/1253/11/01, there had been a clear shift in views regarding the role of NRT with more emphasis on the importance of the clinical benefits of relief of craving and withdrawal symptoms, to the point that NRT indications were not restricted solely to quit rates, although abstinence was the preferred goal. In 2006 the Regulatory Authority authorised a temporary abstinence indication and in 2009 had approved a 'harm reduction' indication on one of Johnson & Johnson's nicotine products.

Cochrane only relevant for long-term quit rates not symptom relief

Regarding the quotations above from Johnson & Johnson's complaint, Cochrane (Stead *et al* 2009) explicitly focused on long-term (at least 6 months) cessation rates as the outcome of interest; in the context of craving relief therefore Cochrane was irrelevant.

In the only head-to-head study of NiQuitin 21mg patch and Nicorette 15mg 16hr patch, it was not only craving and symptom control that was greater with the NiQuitin 21mg patch, but also abstinence, although no claims were made in this regard (Shiffman *et al* 2000). This study was not included in the Cochrane review as it did not report long-term quit rates, only short-term ones. However it was useful to demonstrate the possible link between differing pharmacokinetic and clinical outcomes in terms of craving control and symptom relief. Thus it was irrelevant to quote Cochrane 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch…' to make the argument that there was no evidence to support superior clinical efficacy as craving control and symptom relief were not within the remit of the Cochrane review but were valid clinical outcomes. GlaxoSmithKline Consumer Healthcare's materials accurately represented the level of evidence available and did not claim or imply superior long-term quit rates.

With regard to the ruling of a breach of Clause 7.2 in Case AUTH/1253/11/01, GlaxoSmithKline Consumer Healthcare understood of that ruling that discussion of pharmacokinetics, craving relief and quit rates in the same item was not prohibited, but that these discussions must be presented in such a way that pharmacokinetic profiles were not taken to imply a difference in long-term quit rates between patches. Each item must be considered on its own merits and GlaxoSmithKline Consumer Healthcare considered the leaflet in question sufficiently different such that it did not breach any previous undertaking.

In both the letter and the leaflet the discussion on pharmacokinetics and craving relief was clearly separate from the discussion of quit rates and there were no claims that one impacted the other. The flow and separation of the information were in line with GlaxoSmithKline Consumer Healthcare's previous undertakings and did not imply that the pharmacokinetic differences were of clinical significance in terms of long-term quit rates compared with other patches.

Thus GlaxoSmithKline Consumer Healthcare refuted Johnson & Johnson's allegation of implied clinical superiority in relation to long-term quit rates and a breach of Clause 7.2. GlaxoSmithKline Consumer Healthcare also refuted the implied breach of Clause 25.

Additional comments

Johnson & Johnson noted that in inter-company dialogue, GlaxoSmithKline Consumer Healthcare did not deny that the mailing was presented in such a way that could mislead the reader into believing that differences in pharmacokinetic profile related to differences in smoking cessation outcomes. While GlaxoSmithKline Consumer Healthcare did not explicitly deny this allegation, it was implicit in its response that it refuted it. This point could have easily been further clarified by inter-company dialogue.

Johnson & Johnson went on to cite a statement by GlaxoSmithKline Consumer Healthcare about Tonnesen *et al* and asserted that it used the trial to justify the alleged link between pharmacokinetic data and cessation rates. Johnson & Johnson had used the quotation out of context and as such had misrepresented GlaxoSmithKline Consumer Healthcare's position. Tonnesen *et al*, one of the largest randomised clinical trials of NRT, conducted by Johnson & Johnson's predecessor company, Pharmacia, was discussed in response to the implication that reporting of pharmacokinetic data was not of relevance or value to health professionals.

In making the general case for the relevance of pharmacokinetic data to health professionals GlaxoSmithKline Consumer Healthcare discussed the findings of Tonnesen *et al* which included a dose-response effect for long-term efficacy and suppression of tobacco withdrawal symptoms. Contrary to Johnson & Johnson's statement that 'Tonnesen *et al* did not provide any information relating to the pharmacokinetic profiles of the patches tested', the paper reported 'Plasma nicotine concentrations for the four nicotine patch arms for successful subjects (point prevalence) who used the patch every day'. Tonnesen *et al* compared 15mg/16hr with 25mg/16hr (achieved by 15mg/16hr + 10mg/16hr) nicotine transdermal patches and found a dose response effect. The most logical explanation for this was the pharmacokinetic profile. Thus the general case was made for the relevance of pharmacokinetic data. However, GlaxoSmithKline Consumer Healthcare continued to acknowledge that direct comparative studies were not available for long-term quit rates between the two nicotine transdermal patches marketed by the respective companies and maintained that no claims had been made in that regard and no previous undertakings had been breached in that respect.

It was, however, important that prescribers knew that there were clinical differences in the craving relief offered by different patches in some populations (Shiffman *et al* 2000) and this would affect patient experience. There was interest in how this difference in craving relief might be achieved and as such, pharmacokinetic data were of interest and relevance to prescribers.

Health professionals had a duty to understand the

products they prescribed and recommended and pharmacokinetic profiles were a fundamental part of that understanding.

PANEL RULING

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that its response on this point covered both the leaflet and covering letter. The Panel noted that whilst the leaflet might be read in light of the comments in the covering letter each had to be capable of standing alone as regards the requirements of the Code. The Panel noted that Johnson & Johnson's allegations concerned the leaflet and were considered accordingly. The Panel noted that, nonetheless, some of its rulings might be relevant to the covering letter.

The Panel noted that when the leaflet was fully open three consecutive pages compared NiQuitin 21mg patch with other NRT patches. The left hand page featured the single dose pharmacokinetic data described at Point A1, above. The central page, headed 'Continuous daily use' featured a prominent graph comparing the plasma nicotine concentrations measured over 3 days' use of NiQuitin 21mg patch, Nicorette 15mg patch or Nicotinell 21mg patch. The claim 'By building on the previous 24 hours of delivery, NiQuitin 21mg Clear Patch delivers 30% higher blood levels of nicotine once steady state is reached, compared to day one' appeared above the graph. A claim beneath 'Smoking lapses are more likely to occur on the days morning cravings are elevated' was referenced to Shiffman *et al* (1997); it was then stated that 'NiQuitin 21mg 24-hour patch provides more effective protection against morning cravings and cravings throughout the day, than Nicorette 15mg 16-hour patch' referenced to Shiffman and Ferguson (2008). The next page was headed 'Proven short- and long-term quit rates' which compared the quit rate and efficacy of NiQuitin 21mg Patch with other NRT patches. With regard to quit rates this section claimed that no other patch had been shown to be more effective at 4 and 52 weeks including the Nicorette 25mg Invisipatch.

The Panel did not accept GlaxoSmithKline Consumer Healthcare's submission that the leaflet had three distinct sections and that none of the three sections was a sub section to another. Each page featured a common colour scheme and design format such that the reader's eye was naturally drawn from left to right across the three pages; from the pharmacokinetic data to the clinical claims regarding short- and long-term quit rates.

The Panel noted that Johnson & Johnson's complaint was that the leaflet presented pharmacokinetic data in such a way as to imply superiority in terms of smoking cessation outcomes for the NiQuitin 21mg patch over other NRT patches in particular the Nicorette 25mg patch. The complaint was not about differences in cigarette cravings or nicotine withdrawal symptoms.

The Panel noted that the three page spread of the leaflet presented, from left to right, single dose pharmacokinetic data (discussed at Point A1 above), multiple dose pharmacokinetic data (both of which implied advantages for NiQuitin 21mg patch in terms of AUC, C_{max} and T_{max}) and then a page headed 'Proven short- and long-term quit rates'. In the Panel's view it was not unreasonable that readers might assume that the proven short- and long-term quit rates were as a direct consequence of the apparently favourable pharmacokinetic profiles depicted on the previous two pages. Given that the pharmacokinetic data implied advantages for the NiQuitin 21mg patch then it might be expected that the product produced better clinical results in terms of quit rates which was not so. Claims on the third page of the three-page spread noted and highlighted the percentage of short-term and long-term quitters on NiQuitin 21mg patch (~60% and ~20% respectively). In the Panel's view the use of highlighted figures implied an advantage for NiQuitin 21mg patch whereas it was possible that all NRT patches might result in quit rates of ~60% and ~20% at 4 and 52 weeks respectively. Indeed, under each of the claims it was stated that no other patch had been found to be more effective. In that regard the Panel noted that the Cochrane Review of 2008 had found no evidence of a difference in effect between 16 hour and 24 hour patches.

The Panel considered that whilst readers might find pharmacokinetic data useful care must be taken not to present such data in a way that implied consequential clinical benefits unless a direct link between the two had been established. The Panel considered that the leaflet was misleading as alleged on this point; it implied that the differences in pharmacokinetic profiles led to differences in quit rates and this had not been proven. A breach of Clause 7.2 was ruled.

The Panel noted that Johnson & Johnson had also referred to Case AUTH/1253/11/01 wherein the claim 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette patch', referenced to Fant *et al* was ruled in breach of Clause 7.2. In Case AUTH/1253/11/01 the Panel had noted that Fant *et al* was a pharmacokinetic study not an efficacy study. The claim at issue in that case followed a comparative efficacy discussion and, in the opinion of the Panel, implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more smokers being able to successfully quit than with Nicorette. This was not known. The claim was considered misleading in this regard.

Turning to the present case the Panel noted that there were some differences between Case AUTH/1253/11/01 and the leaflet presently at issue. However, both presented pharmacokinetic data from Fant *et al* including a graph depicting comparative nicotine concentrations. The Panel noted its ruling above of a breach of the Clause 7.2 in the present case as it had been implied that the differences in

pharmacokinetic profiles resulted in differences in quit rates. In that regard the Panel thus considered that the leaflet in question was in breach of the undertaking given in Case AUTH/1253/11/01. A breach of Clause 25 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. Failure to comply with the undertaking in this instance brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

3 Abstinence at 4 weeks

Page 5 (the third page of the three-page inside spread) was headed 'Proven short- and long-term quit rates' and featured two claims in highlighted boxes. The first claim read '~60% of abrupt quitters remain quit at 4 weeks with NiQuitin 21mg Clear Patch'. This claim was referenced to a publication by the Transdermal Nicotine Study Group (TNSG) (1991) and a poster by Shiffman *et al* (2002), presented at the Society for Research on Nicotine and Tobacco in Spain.

COMPLAINT

Johnson & Johnson noted that the TNSG publication reported the results from two multicentre, controlled clinical trials using 21, 14 or 7mg patches over 24 hours. The two studies were randomised, double-blind, placebo-controlled, parallel group trials of 6 weeks' duration and included 935 patients. Successful abstainers were then entered into a third trial for weaning (6 weeks) and off-drug follow up (12 weeks). Short-term abstinence rates for the two trials were measured as smoking cessation during the last 4 weeks of the 6 week full dose period. Abstinence at 6 weeks was 61%, 48%, and 27% for the 21mg, 14mg and placebo patches respectively. The main outcome measure repeatedly referred to in the paper was 4 weeks of continuous abstinence measured at 6 weeks, not smoking cessation measured at 4 weeks.

Shiffman *et al* (2002) reported data from two studies. The first was the TNSG study referred to above and the second was a study comparing nicotine lozenge with placebo. As already stated, the main outcome measure for the TNSG study was abstinence at 6 weeks.

GlaxoSmithKline Consumer Healthcare confirmed that the outcome measure for the TNSG study was 4 weeks' continuous abstinence measured at 6 weeks. Therefore, Johnson & Johnson alleged that the claim that '~60% of abrupt quitters remain quit at 4 weeks with NiQuitin 21mg Clear Patch' was inaccurate and hence misleading in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that four week quit rates were a routine measure used by NHS Stop Smoking Services and would be familiar to readers. Within the NHS, 4 week quit rates were measured up to six weeks after the quit date (West 2005). Similarly in the TNSG study four week quit rates were carbon monoxide (CO) verified continuous abstinence measured at 6 weeks. This meant that the first couple of weeks of the study did not count towards the measurement of the 4 week quit rate. GlaxoSmithKline Consumer Healthcare used the phrase 'remain quit' to convey the message of continuous abstinence rather than point prevalence which would not have required the participants to have been abstinent for the entire 4 weeks.

Quit rates declined over days and weeks as participants lapsed, so the continuous abstinence quit rates were higher the earlier in the quit attempt that they were measured. Johnson & Johnson did not dispute that 60% were still quit at 6 weeks. Since this was measured by continuous abstinence during the previous 4 weeks, then those ~60% must also have been quit 2 weeks earlier at 4 weeks from baseline. Whichever way it was interpreted it was true that ~60% abrupt quitters remained quit at 4 weeks with NiQuitin 21mg patch.

The target audience for the leaflet was familiar with 4 week quite rates and how they were measured up to 6 weeks.

Thus GlaxoSmithKline Consumer Healthcare denied the alleged breach of Clause 7.2.

PANEL RULING

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that readers would be familiar with 4 week quit rates as they were a routine NHS measurement and referred to 4 week quit rates, CO verified continuous abstinence measured at 6 weeks. The Panel noted that the abstinence rates in the TNSG study were CO verified; 61% of subjects were continuously abstinent at the end of 6 weeks; $p \leq 0.001$ vs placebo. The Panel noted that the claim at issue read '~60 of abrupt quitters **remain** quit at 4 weeks …' (emphasis added). The Panel considered that it was thus sufficiently clear that the claim referred to continuous abstinence. The Panel did not consider it misleading to not state that the 4 week data was measured at the 6 week time point. Readers would be familiar with how 4 week quit data was measured. The Panel did not consider that the claim was misleading as alleged; no breach of Clause 7.2 was ruled.

4 Claim 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch'

This claim appeared beneath the claim at issue at Point A3 above within the same highlighted box.

COMPLAINT

Johnson & Johnson stated that the claim at issue was a top parity claim which it understood meant under the Code that there were direct comparative data and hence the NiQuitin 21mg patch had been shown to be at least as effective as other available patches in head-to-head comparisons. This was not so.

Johnson & Johnson noted that GlaxoSmithKline Consumer Healthcare believed that the Code did not require the above claim to be supported with direct head-to-head comparisons. However in Case AUTH/1402/12/02, GlaxoSmithKline Consumer Healthcare complained about a very similar claim made for Nicorette Patch ie 'No other patch is proven more effective at beating cigarettes' and had alleged that '…top parity claims could not be made without head-to-head comparisons with all other patches, which had not been done'. The Panel ruled that the claim implied Nicorette Patch was the most effective patch at beating cigarettes and ruled a breach of the Code.

Johnson & Johnson therefore alleged that the claim at issue was in breach of Clauses 7.2 and 7.3.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that the issues raised were the evidence needed to support a top parity claim and whether a top parity claim could be made under the Code without implying superiority. In Case AUTH/1402/12/02 it was the Panel which ruled that the claim 'No other patch is proven more effective at beating cigarettes' implied superiority. However, each case must be considered on its own merits and in the current environment.

GlaxoSmithKline Consumer Healthcare submitted that, by definition, top parity was not the same as superiority. A superiority claim would state that 'x is more effective than y' and GlaxoSmithKline Consumer Healthcare firmly believed that any manufacturer holding appropriate data to support such a claim would word it in that way. As such a top parity claim would not be used if superiority data were available. A superiority claim could be used to clearly communicate the availability of evidence to show that x was more effective than y, whereas a top parity claim could be used to show that there was no evidence to suggest that other products in the category were any more effective than the product in question. A lack of evidence of a product attribute was not the same thing as evidence of a lack of that product attribute. The differences between a superiority claim and a top parity claim were clear, as illustrated by those used in the leaflet:

Superiority: 'NiQuitin 21mg 24-hour patch provides more effective protection against morning cravings and cravings throughout the day than Nicorette 15mg 16-hour patch'*

Top parity: 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch'

The superiority claim clearly communicated the existence of comparative data and specifically cited those data as a reference. The top parity claim clearly communicated that there were no data that had shown otherwise and as such no reference was cited.

- GlaxoSmithKline Consumer Healthcare noted that this wording had been lifted directly from the leaflet to illustrate the difference between superiority and top parity claims. However GlaxoSmithKline Consumer Healthcare recognised that this claim required the inclusion of the population studied in Shiffman *et al* (2000) in order to comply with previous undertakings.

NRT was only made available on NHS prescription in April 2001 and thus NHS staff exposure to and knowledge of this product area was fairly limited when the previous ruling was made compared with today. In the years since that ruling, there had been significant government investment to developing the NHS Stop Smoking Services, expanding the role of various health professionals in this area. Helping smokers to quit had become much wider than 'prescribers' in the traditional sense. As a result of the introduction of patient group directions and primary care trust voucher schemes the following groups might now be involved in smoking cessation: stop smoking advisors, pharmacists, practice nurses, dentists, midwives, GPs and pharmacy and healthcare assistants. These audiences now received many materials on this therapy area, including promotional materials for NRT. Depending on content and purpose, these materials would have been approved under either the ABPI Code or the Proprietary Association of Great Britain (PAGB) codes. All NRT products had a general sales list (GSL) legal classification and as such were promoted to consumers, non-prescribing health professionals and prescribing health professionals under codes which explicitly allowed top parity claims and had established levels of evidence required to support them. As such, this wide range of health professionals saw materials for the same products approved under the ABPI Code and under other codes, depending on whether their intention was to promote the prescription of the medicine or its recommendation/sale. They would therefore have been frequently exposed to top parity claims and superiority claims in this therapeutic area which straddled over the counter (OTC) and prescription sales.

While the ABPI Code differed from others in that it did not specifically permit top parity claims or provide guidance on the level of evidence needed to support them, there was no clause in the Code that prohibited them. Since the wide range of health professionals in this particular therapeutic area already received materials containing top parity

claims, GlaxoSmithKline Consumer Healthcare considered it reasonable to apply consistency with respect to these types of claim to its health professional audiences, as they would not distinguish between which materials had been approved under which codes. In GlaxoSmithKline Consumer Healthcare's view, if consumers and non-prescribers could be considered able to distinguish between top parity and superiority claims, as evidenced by other codes governing promotion of medicines, this would certainly be true of prescribers, who of course were not isolated from communications containing such claims aimed principally at other audiences.

For the reasons presented above, GlaxoSmithKline Consumer Healthcare considered that in the specific arena of NRT, the top parity claim 'No other patch has been shown to be more effective at 4 weeks…' did not breach the Code and did not mislead the audience. It accurately reflected that there was no evidence to suggest that other nicotine patches were any more effective than NiQuitin patches as assessed by 4 week quit rates. This led to the second point raised by Johnson & Johnson, the data required to support a top parity claim.

It seemed logical to take into account any guidance already provided regarding the substantiation of top parity claims in materials directed at health professionals. Under the PAGB Professional Code, top parity claims were considered valid when the evidence indicated that no other relevant product was superior. Head-to-head, comparative data on all products falling within the scope of comparative statements were not required. Head-to-head data were only required in support of a superiority claim. The same was true for the substantiation of top parity claims in materials aimed at consumer audiences.

The ~60% 4 week quit rate had previously been contested by Pfizer under the PAGB Code and found to reflect the available data by the PAGB and so the complaint was not upheld.

Most studies on nicotine patches looked at long-term (six months plus) quit rates and did not always report earlier quit rates. However, Tonnesen *et al* compared Nicorette 15mg patches with Nicorette 15mg +10mg patches and placebo and reported quit rates at week 4. These were 50.6%, 40.9% and 27.7% for 25mg, 15mg and placebo respectively. Overall, at all time points 25mg was significantly better than 15mg patch. It was on the basis of this study that Johnson & Johnson promoted the 25mg Invisipatch as more effective than its 15mg patch and so therefore one needed only compare 4 week quit rates for NiQuitin 21mg patch with 25mg 4 week quit rates as it was established that the 25mg patch was more effective than the 15mg patch.

Although it was difficult to compare across studies, the relative risks for the NiQuitin 21mg patch vs placebo in a large double blind, placebo controlled trial was 2.26 for the 4 week continuous abstinence rate at 6 weeks (61/27 = 2.26) and 2.1 (19/9 = 2.1) for the one year quit rates (TNSG data). In comparison, the relative risks for the 25mg patch vs placebo in Tonnesen *et al* were 1.82 (50.6/27.7 = 1.82) for the 4 week rate and 1.6 (15.9/9.9 = 1.6) for the one year rate. Thus it could be seen that not only numerically 60% vs 51%, but also in comparing relative risks there was no evidence to suggest that other nicotine patches were more effective than NiQuitin 21mg. GlaxoSmithKline Consumer Healthcare was not aware of any data on 4 week quit rates for Nicotinell 21mg patches.

GlaxoSmithKline Consumer Healthcare asserted that this was an appropriate use of a top parity claim for its products that were promoted for prescription and OTC use and it was directed to an audience frequently exposed to top parity claims. Thus GlaxoSmithKline Consumer Healthcare refuted the alleged breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that whilst top parity claims were not prohibited under the Code care should be taken to ensure that they did not give a misleading impression of a product's relative efficacy, were capable of substantiation and otherwise complied with the Code. Every case had to be considered on its own merits. The context in which a claim appeared was important.

The Panel noted that both parties referred to Case AUTH/1402/12/02 wherein the claims 'No other patch offers smokers a greater chance of success', 'No other patch is proven more effective at beating cigarettes' and 'No other nicotine patch works harder at beating cigarettes …' were ruled in breach of Clause 7.4 by the Panel. The Panel had noted that there was no comparative data on all the available nicotine patches. The claims implied that Nicorette patch was the most effective patch at beating cigarettes. No material or comment in relation to substantiation of the claims was provided. On the data before it the Panel considered that the claims were not capable of substantiation.

Turning back to the case now before it, Case AUTH/2298/2/10, the Panel noted GlaxoSmithKline Consumer Healthcare's submission that there was no evidence to suggest that other nicotine patches were any more effective than NiQuitin patches as assessed by 4 week quit rates. The Panel, however, noted the company's subsequent submission that it was not aware of any data on 4 week quit rates for Nicotinell 21mg patches. In that regard the Panel considered the claim 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch' was misleading. Further, context was important. The Panel considered that the comparative theme of the leaflet meant that the claim at issue was likely to be read as a superiority claim and was thus misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

5 Use of Aubin *et al* (2008) to support a 52 week quit claim

The second highlighted box on the third page of the centre of the leavepiece featured the claim: '~ 20% of quitters remain quit at 52 weeks with NiQuitin 21mg Clear Patch' referenced to Aubin *et al* (2008).

COMPLAINT

Johnson & Johnson noted that there was no reference to the fact that Aubin *et al* was an open-label study which was a critical piece of information that the reader should know. In Case AUTH/2203/1/09, the Panel had stated regarding this study:

> '… whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data.'

In inter-company dialogue GlaxoSmithKline Consumer Healthcare argued that Aubin *et al* was presented as one example, not the data set in its entirety and that this was why the open-label design did not need to be stated. Johnson & Johnson disagreed. No other supporting reference was given and the reader had not been provided with all the necessary information to assess the claim based on the single reference provided. Johnson & Johnson alleged a breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that a one year quit rate of ~20% reflected the data available specific to NiQuitin 21mg patch. It cited Aubin *et al* as one example as the claim itself did not refer to a specific study. It was not the only data available to substantiate the claim, but was an easily accessible, straightforward recent study with which many of the recipients of the leaflet would already be familiar. It appeared in a highly respected, peer reviewed journal, Thorax, and had featured in the NHS prescribing adviser's blog in February 2008 (Robinson 2008) which many of the leaflet's recipients would have read.

Another study of NiQuitin 21mg patch that reported one year quit rates included Richmond *et al* (1997), a randomised, double-blind, placebo-controlled trial in 305 participants. Twelve month quit rates with NiQuitin 21mg patch were around 20% (point prevalence 29%, prolonged abstinence 24% and continuous abstinence 19%).

Another study looked at the additional benefit of NiQuitin 21mg patch on behavioural therapy in 64 participants which achieved one year abstinence rates of 38% in the behavioural therapy plus patch group compared to 22% in those using behavioural therapy alone (Cinciripini *et al* 1996).

Cruse *et al* (2001), an open, observational study following smoking cessation in the workplace using NiQuitin patches and found 20% were non-smokers at the 12 month follow up (15% continuous abstinence plus 5% who had lapsed but had since quit successfully). Case AUTH/2203/1/09 was not relevant here. In that case the claim in question was a superiority claim for Champix vs NRT where Aubin *et al* was the only data available and being used to support the superiority claim in its entirety. In the current case, Aubin *et al* was cited simply as an example of a 20% quit rate but with data from a randomised, double-blind, placebo-controlled trial available to confirm this finding and substantiate the claim further if required.

The claim was supportable by the body of evidence and was not misleading. GlaxoSmithKline Consumer Healthcare refuted the alleged breach of Clause 7.2.

PANEL RULING

The Panel noted each party's submission about Aubin *et al* and Case AUTH/2203/1/09 wherein Aubin *et al* was the sole data set to support a superiority claim for varenicline vs NRT. The Panel considered that the present case was different. Aubin *et al* was being used for its NRT results and there was other data including Richmond *et al*, a randomised, placebo-controlled trial, to the support claim at issue. The Panel considered that the claim '~20% of quitters remain quit at 52 weeks with NiQuitin 21mg Clear Patch' was not misleading as alleged. No breach of Clause 7.2 was ruled.

6 Claim 'No other patch has been shown to be more effective at 52 weeks, including Nicorette 25mg Invisipatch'

This claim appeared beneath the claim considered in Point A5 above, within the same highlighted box.

COMPLAINT

For the same reasons described above at Point A4, Johnson & Johnson alleged that the claim that 'No other patch has been shown to be more effective at 52 weeks…' implied superiority for the NiQuitin 21mg patch over other patches. As already stated, there were no head-to-head studies showing that the NiQuitin 21mg patch was more effective than marketed patches. For the reasons outlined above breaches of Clauses 7.2 and 7.3 were alleged.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that the same principles applied as discussed in Point A4 and Johnson & Johnson again supplied no evidence to refute the claim as it stood, but believed a top parity claim would be

misunderstood by the readers to mean that NiQuitin 21mg patch was superior to other patches in terms of long-term quit rates. For the reasons previously stated, GlaxoSmithKline Consumer Healthcare asserted that this was an appropriate use of a top parity claim for GSL products that were promoted for prescription and OTC use and it was directed to an audience which was frequently exposed to top parity claims.

The Cochrane Review 2008, as cited by Johnson & Johnson, selected only randomised trials where NRT was compared with placebo or no treatment, or where different doses of NRT were compared. Trials which did not report cessation rates and those with a follow-up of less than 6 months were excluded. The results of the review stated 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

Thus while direct comparative data were not available to prove equivalence or superiority, a large-scale meta-analysis of indirect comparative data showed no evidence to suggest any other patch was more effective than NiQuitin 21mg patch as assessed by long-term quit rates. Hence a superiority claim could not be made but the top parity claim was valid. Thus GlaxoSmithKline Consumer Healthcare refuted alleged breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the Cochrane Review 2008 stated 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'. The Panel considered its comments at Point A4 above about context and the comparative theme of the leaflet were nonetheless relevant. The Panel considered that given the comparative nature of the leaflet the claim was likely to be read as a superiority claim and was thus misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

B Covering letter

The covering letter was headed 'Which therapeutic nicotine patch delivers more nicotine faster than any other patch?' and began by discussing the pharmacokinetic data at issue in Point A1 above. Subsequent paragraphs discussed morning cravings and general effectiveness.

1 Claim 'Reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch'

This claim appeared as the first of two bullet points near the start of the letter.

COMPLAINT

Although the graph within the leaflet appeared to support this claim, as discussed above, Johnson & Johnson had been unable to verify the values given by GlaxoSmithKline Consumer Healthcare for the comparative C_{max} values and it had not been made clear whether these differences were statistically significant. Irrespective of statistical significance, C_{max} was of minimal clinical relevance for nicotine patches. As stated above nicotine patches were designed to deliver steady levels of nicotine over a prolonged period of time. Inclusion of this claim, particularly in such a prominent position in the letter, implied that this data was relevant to the clinical scenario and that the prescriber should take this into account when deciding to prescribe NiQuitin 21mg patch rather than Nicorette 25mg Invisipatch.

In inter-company dialogue, GlaxoSmithKline Consumer Healthcare stated that it believed that the delivery characteristics of the patch were fundamental to its clinical success. However, as already stated, Johnson & Johnson was not aware of any data to suggest that the NiQuitin 21mg patch was superior in terms of clinical success compared with Nicorette 25mg patch.

There were no data whatsoever to suggest that time to peak plasma concentration was of any relevance to the choice of which patch to prescribe. The parameter of peak plasma level was given undue prominence in the letter suggesting that it was clinically important. This was not the case. Therefore, Johnson & Johnson believed that this claim was misleading and a breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson had asserted that it was unclear whether C_{max} values for NiQuitin 21mg vs Nicorette 25mg were statistically significant despite this being confirmed in inter-company dialogue. However GlaxoSmithKline Consumer Healthcare considered this was a specious argument as no claims was made about C_{max} itself. As mentioned above, the claim was that NiQuitin 21mg patch 'Reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch' and this was unambiguously supported by the substantial difference in the time to reach peak concentrations between the two patches (6 hours vs 12 hours; $p<0.0001$) (Geiss *et al* 2010).

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson further stated that peak plasma level was given undue prominence in the letter suggesting it was clinically important. The first half of the allegation was untrue. The claim 'Reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch' appeared only once in the letter and peak plasma levels were not discussed further. Neither did the letter discuss the actual peak plasma concentrations reached. This was hardly undue prominence.

The second half of Johnson & Johnson's sentence asserted that the claim was not clinically relevant. GlaxoSmithKline Consumer Healthcare firmly considered that the pharmacokinetic profile of nicotine delivery systems was of fundamental clinical relevance, as discussed at length in inter-company dialogue. There was no definitive therapeutic level defined for nicotine, whereby one could reliably predict efficacy either in terms of craving, symptom control or abstinence. The threshold for efficacy might vary across individual smokers and at various times during the quitting process. However, it was recognised that there was a dose-response curve for transdermal nicotine patches (as illustrated and discussed in Tonnesen *et al* comparing 15mg and 25mg dosing, and the TNSG trial comparing 21mg, 14mg and 7mg patches). As such, to reach an effective level more quickly (whatever that level was) meant less time at sub-optimal levels and aided morning symptom relief even during the first few days of a quit attempt (Shiffman *et al* 2000), the most difficult days for quitters (Garvey *et al* 1992). Health professionals had a duty to be informed about the products they recommended or prescribed and pharmacokinetics were reported for all relevant products in the licensed details for this very reason. C_{max} and T_{max} were both explicitly discussed even in the Nicorette Invisipatch SPC indicating their relevance and importance to health professionals.

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson also stated that it was not aware of any data to suggest that the NiQuitin 21mg patch was superior in terms of clinical success compared with Nicorette 25mg patch'. No superiority claims were made in this regard. GlaxoSmithKline Consumer Healthcare referred to Point A2 above for further discussion on the relevance of discussing pharmacokinetic data with health professionals.

Thus GlaxoSmithKline Consumer Healthcare refuted the alleged breach of Clause 7.2.

PANEL RULING

The Panel considered its comments at Point A2 about the pharmacokinetic data and clinical outcome were relevant here. The consequential link between the pharmacokinetic data and the clinical claims had not been established. A reader would not unreasonably assume that the favourable pharmacokinetic data led to the favourable clinical data discussed subsequently in the letter; effective relief from morning cravings and effectiveness at 4 and 52 weeks. The causal link had not been established and the claim was misleading in this regard. A breach of Clause 7.2 was ruled.

2 The effect of nocturnal nicotine dosing on cravings

The letter contained the following paragraph:

'16-hour patch wear means that blood nicotine concentrations drop to minimal levels overnight when the patch is removed and may be why NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15mg 16-hour patches. Even though most lapses happen later in the day, they are more likely to occur on the days when morning cravings are elevated'.

COMPLAINT

Johnson & Johnson believed that the suggestion that nocturnal nicotine dosing with the 24-hour patch '…may be why NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15 mg 16-hour patches' was speculation. Johnson & Johnson was not aware of any robust data demonstrating that wearing a patch overnight was related to improved cravings scores throughout the day. There could be a number of reasons to explain differences between the 21mg 24 hour patch and 15mg 16 hour patch in cravings relief including difference in overall strength between the two.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare cited the NiQuitin 21mg patch SPC which stated: 'Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings'. This statement related to morning cravings. It did not support the claim at issue which suggested that nocturnal nicotine dosing might provide more effective protection against cravings throughout the day. Therefore, Johnson & Johnson alleged a breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson asserted that the claim was 'pure speculation', however, it had not provided any evidence to refute the suggestion that nocturnal nicotine dosing might be related to an improvement in cravings throughout the day. The letter was written in such a way that it offered a possible explanation for the improved craving control seen with 24 hour patch wear. Improved craving control compared to a 16 hour patch was seen not only in mornings but also throughout the day in heavily dependent smokers (smokers who smoked within 30 minutes of waking and had their worst cravings in the morning) as reported in Shiffman *et al* (2000).

The claim at issue was written as postulation (using the phrase 'may be why') and did not categorically state that this was the only possible explanation.

The regulatory authorities had agreed that 24-hour wear of NiQuitin patches (all strengths ie 21mg, 14mg and 7mg) optimised the effect against morning cravings as stated in the SPCs. They therefore agreed that it was not simply the strength

of the patch that affected craving control, but the duration of application. This finding was relevant and robust enough to form part of the licensed particulars so it was baffling that Johnson & Johnson appeared to dismiss it.

GlaxoSmithKline Consumer Healthcare refuted the alleged breach of Clause 7.2.

PANEL RULING

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that the claim at issue was written as postulation and did not state that 24-hour patch wear was the only possible explanation. The Panel further noted GlaxoSmithKline Consumer Healthcare's submission that Johnson & Johnson had not provided any data to refute the suggestion that nocturnal dosing might be related to an improvement in cravings throughout the day. The Panel noted that claims had to be capable of substantiation.

The Panel noted that the NiQuitin 21mg patch SPC stated that use for 24 hours was recommended to optimise effect against morning cravings. The claim at issue related to 'protection against cravings throughout the day'.

The Panel noted that the only data showing improved craving control throughout the day for the 24-hour patch was for heavily dependent smokers rather than the general smoking population (Shiffman *et al* 2000). The Panel considered that the phrase 'may be' was insufficient to negate the impression that nocturnal nicotine dosing did provide more effective protection against cravings throughout the day in the general smoking population. This impression was compounded by the subsequent paragraph which referred to optimizing protection against morning cravings (in line with the SPC) and providing a level of nicotine in the blood stream on waking that could be built on with the application of the next patch. A subsequent claim referred to NiQuitin 21mg patch's general effectiveness compared to other patches. The Panel considered the claim at issue misleading as alleged. A breach of Clause 7.2 was ruled.

3 Implied greater smoking cessation efficacy based on cravings data

COMPLAINT

Johnson & Johnson was concerned that the paragraph referred to at Point B2 above represented breaches of the Code including a breach of a previous undertaking.

The first claim '… NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15mg 16-hour patches' was referenced to Shiffman *et al* (1997) (reference 3). The second claim 'Even though most lapses happen later in the day, they are more likely to occur on the days when morning cravings are elevated' was referenced to Shiffman and Ferguson (2008) (reference 4).

Shiffman *et al* (1997) was a non-comparative study which assessed urge and lapse in smokers who had recently quit. It did not demonstrate that the NiQuitin 21mg patch provided more effective protection against cravings than the Nicorette patch. GlaxoSmithKline Consumer Healthcare had acknowledged that the referencing was wrong and agreed to correct this in future iterations. Johnson & Johnson assumed that references 3 and 4 had been mixed up.

Shiffman and Ferguson was an analysis of two randomised clinical studies. The studies and the analyses were sponsored by SmithKline Beecham. The first of the two studies cited compared a 21mg 24 hour patch with a placebo patch (n=102) while the second study compared a 21mg 24 hour patch with a 15mg 16 hour patch (n=244). Overall the authors concluded that the first study showed that the 21mg patch was effective in reducing cravings throughout the day compared with placebo and that the second study showed that cravings were lower at all times during the day with the 21mg patch compared with the 15mg patch.

Johnson & Johnson noted that in Case AUTH/1401/12/02, the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' was ruled in breach of Clause 7.3 by the Panel and upheld on appeal. It was alleged that the claim contributed to the overall impression that 24 hour patches had greater efficacy in achieving smoking cessation than 16 hour patches. There were no data available at the time to show clinical differences between 16 and 24 hour patches and this situation had not changed. Indeed, the 2008 Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation stated that 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

In the letter now at issue, Johnson & Johnson believed that the reader would assume that the stated reduction in cravings throughout the day apparently achieved with 24-hour patches was such that NiQuitin 21mg patch had greater efficacy in achieving smoking cessation compared with the 16 hour patch. This was compounded by the link to lapses in the proceeding claim.

Moreover, Shiffman *et al* (1997), which Johnson & Johnson believed was the reference GlaxoSmithKline Consumer Healthcare intended to use to support the claim that morning cravings and lapses were linked (this was the case for the accompanying leaflet), was conducted in smokers who had recently quit and were not using

pharmacotherapy to treat their nicotine withdrawal. There was no evidence to suggest that the pattern of cravings and lapses was the same as for the patients being treated with NRT.

Therefore, for all the reasons cited, Johnson & Johnson believed that these claims were in breach of Clause 7.2. It also believed that the implication that improvements in cravings relief were associated with higher smoking cessation outcomes was a breach of undertaking and therefore a breach of Clause 25.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that as agreed in inter-company dialogue, the referencing was incorrect and it had committed to correcting it. The material in question cited Shiffman *et al* (1997) and Shiffman and Ferguson respectively in support of the above claims. The references, however, were cited in the wrong order.

GlaxoSmithKline Consumer Healthcare noted that in Case AUTH/1401/12/02, a breach of the Code was ruled with regard to the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' and upheld on appeal. The Panel considered that linking morning cravings and relapse to a conclusion to recommend NiQuitin to help them quit 'from the word go' resulted in the reader assuming the stated reduction in morning cravings was such that NiQuitin had greater efficacy in achieving smoking cessation compared with the 16-hour patch. The Appeal Board noted that the claim implied that because NiQuitin was effective in relieving morning cravings, it would also be effective in long-term smoking cessation. It also considered that 'from the word go' appeared to differentiate NiQuitin from 16-hour patches. Taken together, these statements implied that NiQuitin 24-hour patch was more likely to help a patient stop smoking than a 16-hour patch and thus overstated the data.

Similar principles applied to those discussed in Point A2 above. While the material in question discussed pharmacokinetics, cravings and quit rates, it did so in line with previous undertakings and made no claim that implied either the pharmacokinetic profile of the NiQuitin 21mg/24hr patch or the craving relief it provided resulted in superior long-term quit rates compared with other patches.

The letter discussed the new pharmacokinetic data for NiQuitin 21mg/24hr compared with Nicorette 25mg/16hr patches, followed by a comparison of craving relief (not quit rates) between NiQuitin 21mg/24hr and Nicorette 15mg/16hr in a separate paragraph. This was followed by the relief of morning cravings by 24 hour wear of NiQuitin 21mg/24hr patch, and that was followed by a sentence on quit rates that specifically did not state that quit rates were higher with NiQuitin 21mg patch. The headline and highlighted take out message from the letter was that NiQuitin 21mg Clear Patch delivered more nicotine than other patches, not that it had higher quit rates. The reader was then referred to the enclosed leaflet for further information on the new data, below which was the headline claim for that study.

The letter was sufficiently different such that it did not breach a previous undertaking. Thus GlaxoSmithKline Consumer Healthcare refuted an alleged breach of Clause 7.2 and of Clause 25 with respect to the undertaking given in Case AUTH/1401/12/02.

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson also alleged that there was no evidence to suggest that the pattern of cravings and lapses reported in Shiffman *et al* (1997) (for smokers who had recently quit without pharmacotherapy) was the same for patients being treated with NRT and therefore questioned GlaxoSmithKline Consumer Healthcare's assertion that morning cravings and lapses were linked in the context of smokers quitting with NRT. However, Johnson & Johnson had provided no evidence to the contrary. Studies of NRT using a placebo comparator showed the same pattern of craving and lapse in both groups although the magnitude and frequency of craving and lapse was less in the active group. Figure 1 in Shiffman and Ferguson, illustrated this in terms of craving. This provided *prima facie* support that the findings of Shiffman *et al* (1997) were also relevant to those using NRT.

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson also stated that while GlaxoSmithKline Consumer Healthcare agreed to amend claims in response to points raised on the leaflet, it failed to acknowledge breaches of the Code for the covering letter. GlaxoSmithKline Consumer Healthcare noted that in its response to Johnson & Johnson it agreed that a breach of undertaking relating to Case AUTH/1253/11/01 had occurred with respect to the requirement to include the details of the subgroup studied in Shiffman *et al* (2000) and therefore stated in the section of the response dealing with the mailing that the claims beneath the graph would be amended to ensure compliance. Implicit within this was that the claims would be amended, irrespective of the material on which they were to appear. Also of note was that the covering letter was bespoke to the mailing and certified as part of the same item, as indicated by the reference number. Indeed, in its complaint Johnson & Johnson acknowledged that GlaxoSmithKline Consumer Healthcare '…agreed to withdraw the items and confirmed that it would make corrections to address a number of our concerns…' and '…also agreed to stop using any similarly affected materials'. It was clear from these statements that Johnson & Johnson was in no doubt as to GlaxoSmithKline Consumer Healthcare's intended action and GlaxoSmithKline Consumer Healthcare was therefore unsure as to why Johnson & Johnson had included this point in its complaint.

Overall GlaxoSmithKline Consumer Healthcare accepted a breach of Clause 25 with respect to the undertaking given in Case AUTH/1253/11/10, to clearly state the patient population studied when making comparative craving relief claims between NiQuitin 21mg/24hr patches and Nicorette 15mg/16hr patches based on Shiffman *et al* (2000). GlaxoSmithKline Consumer Healthcare took this extremely seriously and the measures subsequently taken had been detailed in the covering letter. GlaxoSmithKline Consumer Healthcare refuted all other allegations made by Johnson & Johnson of breaches of Clauses 7.2, 7.3 and 25.

PANEL RULING

The Panel noted Johnson & Johnson's allegation that there was no evidence to suggest that the pattern of cravings and lapses in Shiffman *et al* (1997) applied to patients being treated with NRT. The Panel did not accept that Figure 1 in Shiffman and Ferguson provided *prima facie* support as suggested by GlaxoSmithKline Consumer Healthcare; it depicted placebo-controlled data. The study authors noted that smoking lapses commonly occurred in the evening and late night hours but the authors did not observe higher craving during these time periods. The authors noted that many studies had shown that smoking lapses were associated with acute increases in craving when smokers experienced provocative situations and thus the occurrence of such lapses during the evening and night hours might be due to exposure to such stimuli rather than to any inherent diurnal rhythm in the intensity of background craving. The Panel considered the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that in Case AUTH/1401/12/02 it was alleged that the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' inferred a greater likelihood of success in smoking cessation with a 24-hour patch than with a 16-hour patch. The Appeal Board, *inter alia*, considered that the claim implied that because NiQuitin CQ was effective in relieving morning cravings, it would also be effective in long-term smoking cessation. The phrase 'from the word go' appeared to differentiate NiQuitin CQ from the 16-hour patches referred to in the preceding paragraph. The Appeal Board considered that the claim implied that NiQuitin CQ 24-hour patch was more likely to help a patient to stop smoking than a 16-hour patch. The Appeal Board considered that the claim overstated the data and was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2.

Turning to the present case, Case AUTH/2298/2/10, the Panel noted that there were some differences between the paragraph at issue and the claim considered previously. Nonetheless, the Panel considered that the claims at issue implied that as lapses were more likely to occur when morning cravings were elevated, the more effective protection against cravings afforded by the 24-hour patch meant that NiQuitin 21mg patch was more likely to help a patient stop smoking than a 16-hour patch. There was no evidence this was so. This impression was misleading, a breach of Clause 7.2 was ruled. Further this impression was contrary to the undertaking given in Case AUTH/1401/12/02 and thus a breach of Clause 25 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. Failure to comply with the undertaking in this instance bought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

4 Claim 'No other patch is proven more effective than NiQuitin 21mg Clear Patch at 4 or 52 weeks'

COMPLAINT

Johnson & Johnson noted that this claim in the letter was very similar to the claims about short- and long-term quit rates in the leaflet.

Johnson & Johnson alleged, as described above, that the claim implied superiority in terms of cessation rates for the NiQuitin 21mg patch over other patches. This was not the case and therefore Johnson & Johnson believed that this claim was in breach of Clauses 7.2 and 7.3.

RESPONSE

GlaxoSmithKline Consumer Healthcare did not specifically respond to this point.

PANEL RULING

The Panel considered that its rulings above at Points A4 and A6 were relevant here. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **23 February 2010**

Case completed **14 June 2010**