CASE AUTH/2362/10/10

BOEHRINGER INGELHEIM v NOVARTIS

Promotion of Onbrez

Boehringer Ingelheim complained about a leavepiece for Onbrez Breezhaler (indacterol inhalation powder) issued by Novartis. Onbrez was indicated for maintenance bronchodilator treatment of airflow obstruction in adults with chronic obstructive pulmonary disease (COPD). The recommended dose for inhalation was the content of one 150mcg capsule once a day; the inhalation of the content of one 300mcg capsule once a day had been shown to provide additional clinical benefit with regard to breathlessness, particularly in patients with severe COPD.

The detailed response from Novartis is given below.

Boehringer Ingelheim alleged that the term 'strength' in the claim 'Sustained strength that helps your patients with COPD meet the varied demands of daily life' was too generalised to substantiate. This was not a meaningful clinical indicator and did not help the prescriber judge when or how to use Onbrez.

The Panel noted that the front cover of the leavepiece was headed 'NEW Onbrez Breezhaler: the first 24 hour [long-acting beta$_2$-agonist] for COPD' and featured the picture of a lion apparently leaping, full stretch, from an inhaler device. The headline above the picture was 'Sustained strength that helps your patients with COPD meet the varied demands of daily life'. The Panel considered that the unqualified use of the word 'strength' was misleading; there was no indication as to what, in that context, 'strength' meant. The Panel noted Novartis' submission that 'strength' related to significant clinically meaningful efficacy in a given disease state and in that regard considered that 'strength' could be applied to all medicines. The Panel queried Novartis' submission that in the context of COPD health professionals would equate 'strength' with efficacy in terms of markers for lung function. The Panel considered that the strong, unqualified claim was misleading and, in that regard, could not be substantiated. The Panel also considered that the unqualified use of the word 'strength' implied some special property which could not be substantiated. Breaches of the Code were ruled. The Panel did not consider that the unqualified use of 'strength' was such that it did not help prescribers judge when or how to use Onbrez. No breach of the Code was ruled.

Boehringer Ingelheim alleged that in the strapline 'Sustained relief in COPD' which appeared below the Onbrez product logo, relief from what was not made clear.

The Panel noted that Onbrez was the first long-acting beta$_2$-agonist for COPD. Section 5.1 of the SPC stated that 'The 24-hour bronchodilator effect of Onbrez Breezhaler was maintained from the first dose throughout a one-year treatment period with no evidence of loss of efficacy'. The Panel noted that Onbrez was indicated for maintenance of bronchodilator treatment of airflow obstruction in adults with COPD. The Panel considered that shortness of breath would be a major presenting symptom of COPD. In that regard the Panel did not consider that the strapline 'Sustained relief in COPD' was misleading as alleged; the claim could be substantiated and did not exaggerate the medicine's properties. No breach of the Code was ruled.

Boehringer Ingelheim alleged that the use of an asterisked footnote to qualify the claim 'Rapid bronchodilation* within 5 minutes that lasts all day' was not adequate. The asterisk referred to the footnote 'Onbrez Breezhaler is not licensed for acute symptomatic relief'.

The Panel noted that the claim was referenced to Vogelmeier *et al* (2009) (INTIME study) and Feldman et al (2009) (INLIGHT– 1 study). Novartis had submitted that the INSURE study (Balint *et al* 2009) also supported the claim for a rapid onset of action. The INTIME study demonstrated that Onbrez had an onset of action within 5 minutes on the first day of dosing. The INLIGHT-1 study authors concluded, inter alia, that Onbrez demonstrated a fast onset (within 5 minutes) of bronchodilation from the first dose and the single dose INSURE study showed that Onbrez significantly increased FEV_1 at 5 minutes post-dose.

The Panel noted that Section 5.1 of the SPC stated that there was a rapid onset of action within 5 minutes after inhalation. It was not clear from the SPC whether this was demonstrated each day when Onbrez was used for long-term therapy.

The Panel noted that COPD was a chronic disease and, as such, patients would require long-term therapy. The Panel noted that studies had shown that rapid bronchodilation was observed with the first dose of Onbrez. Novartis had not submitted data to show that subsequent daily doses of Onbrez also produced rapid bronchodilation within 5 minutes. In any event the Panel questioned the relevance of promoting a short onset of action in a long-term therapy when that long-term therapy was not also indicated for acute use. The Panel considered that the claim was misleading and ruled a breach of the Code.

Boehringer Ingelheim noted the claim

'Improvements in breathlessness at least as effective as salmeterol and tiotropium'. Section 5.1 of the Onbrez SPC, 'Symptomatic benefits', stated, inter alia, that 'The magnitude of response was generally greater than seen with active comparators'. However there was a reference to table 2 of the SPC which included the percentage of patients who achieved the minimal clinically important difference TDI (transition dyspnoea index) – 57% for indacterol and 57% for tiotropium. 'At least as effective', implied possible superiority. Boehringer Ingelheim thus alleged that this was misleading and exaggerated.

Boehringer Ingelheim noted that no reference was made on the same page as the claim to the open label nature of the study design which was also necessary to understand the clinical data. This item did not provide enough information for the prescriber to make informed decisions regarding the clinical data.

The Panel noted that the claim 'Improvements in breathlessness at least as effective as salmeterol and tiotropium' was referenced to Kornmann *et al* (2009) (INLIGHT-2 study) and Donohue *et al* (2010) (INHANCE study). Kornmann *et al* did not show a clinically significant difference in terms of trough FEV_1 and the transition dyspnea index between indacterol and salmeterol. There was a statistically significant advantage for indacterol with regard to rescue-free days. Similarly, Donohue *et al* failed to show a clinically significant difference between indacterol and tiotropium in terms of trough FEV_1 and transition dyspnea index.

The Panel did not consider that the claim at issue reflected the balance of the evidence. The claim implied possible clinical superiority for indacterol whereas in terms of trough FEV_1 and the transition dyspnea index, it had only been shown to be clinically similar to salmeterol and tiotropium. The Panel considered that the claim was misleading as alleged. The Panel further considered that the claim was insufficiently complete such as to enable a prescriber to make an informed decision regarding the clinical data. Breaches of the Code were ruled.

Boehringer Ingelheim noted the claim 'Significantly more patients experienced clinically meaningful improvements in quality of life vs. other bronchodilators'.

There was no reference on the page to the open label nature of the study design which was necessary to understand the clinical data. The leavepiece did not provide enough information for the prescriber to make informed decisions regarding the clinical data.

The Panel noted that the claim was referenced to Kornmann *et al* (IN-LIGHT 2 study) and Yorgancioglu *et al* (2009) (INHANCE study). Kornmann *et al* compared indacterol and salmeterol and reported that indacterol-treated patients had an improved health status with a 2.1 unit difference over salmeterol ($p<0.05$) at week 12. This difference, however, although statistically significant was less than the minimum clinically important difference of 4 points. There was no difference between the two products at week 26.

Yorgancioglu *et al* compared indacterol 150mcg and 300mcg and tiotropium 18mg all given once daily. The tiotropium was administered under open-label conditions. In terms of the percentage of patients achieving a clinically important difference of ≥4 units vs placebo in a health related quality of life score, there was a statistically significant difference between tiotropium and both doses of indacterol at weeks 4 and 8 in favour of indacterol; there was no difference between the medicines at week 12 and at week 26 there was only a statistically significant advantage for the lower dose of indacterol vs tiotropium.

The Panel considered that the claim at issue did not provide enough information about the clinical data as alleged. The Panel did not accept that the fact that another page of the leavepiece stated that the tiotropium study was open-label was sufficient as submitted by Novartis. A breach of the Code was ruled.

Boehringer Ingelheim noted that the claim 'Onbrez Breezhaler: improvements in quality of life in more patients than salmeterol or tiotropium' appeared as the headline on a page which featured a bar chart depicting the results of Yorgancioglu *et al*. The claim was referenced to Kornmann *et al* and Yorgancioglu *et al*.

Boehringer Ingelheim alleged that Novartis had cherry-picked the data to report the improvements in quality of life (QoL) vs tiotropium at 26 weeks. Whilst there were differences in QoL between the indacterol and the tiotropium groups these were small and inconsistent. At weeks 4, 8 and 26 there was a significant improvement in the indacterol group compared with the tiotropium group. However, at 12 weeks there was no significant difference in QoL between the groups.

The Panel noted that Kornmann *et al* reported that at week 12 the percentage of patients who achieved a clinically important improvement in a quality of life score was highest in the indacterol group (57.9%) compared with salmeterol (46.8%) and placebo (39.1%) groups.

The claim headed a page which featured a bar chart which depicted the results at 26 weeks of Yorgancioglu *et al*. The bar chart showed that at week 26, 47.3% of patients treated with tiotropium had a clinically significant improvement in a quality of life measurement vs 57.8% in the indacterol 150mcg treated group ($p<0.01$). There was, however, no significant difference between the percentage of patients achieving a clinically important improvement in the indacterol 300mcg treated group (52.5%) vs the tiotropium group (47.3%).

Yorgancioglu *et al* had shown that at weeks 4, 8 and 26, a statistically significantly greater percentage of patients on indacterol 150mcg achieved a clinically important difference in quality of life vs tiotropium-treated patients (p<0.01). Only at week 12 was there no statistically significant difference between the two treatment groups. Thus, in three out of the four time points measured there had been a statistically significant advantage for indacterol 150mcg vs tiotropium. The Panel further noted Novartis' submission that tiotropium reached its maximal effect in 6 months as evidenced by a peak in FEV_1. The Panel did not consider that to show the 26 week data was 'cherry picking' as alleged. No breach of the Code was ruled.

Boehringer Ingelheim alleged that five small drawings each showing a different step in the correct use of the Breezhaler device which were an abridged version of the instructions for use found in the patient information leaflet and the SPC, implied that the process for use was simpler than it actually was. This was misleading and could cause misunderstandings between patients and prescribers: prescribers might not appreciate that it was necessary to work through a 13 step process.

The Panel noted that the instructions for use had been given in an abbreviated form in the leavepiece; 5 steps had been illustrated compared with the 13 shown in the SPC. The Panel considered that although more instructions would have been helpful, the 5 steps shown were not misleading per se. No breach of the Code was ruled.

Boehringer Ingelheim Limited complained about a six page, gate-folded leavepiece (ref IND10-010) for Onbrez Breezhaler (indacterol inhalation powder) issued by Novartis Pharmaceuticals UK Ltd. Onbrez was indicated for maintenance bronchodilator treatment of airflow obstruction in adults with chronic obstructive pulmonary disease (COPD). The recommended dose for inhalation was the content of one 150mcg capsule once a day; the inhalation of the content of one 300mcg capsule once a day had been shown to provide additional clinical benefit with regard to breathlessness, particularly in patients with severe COPD. Onbrez was the first 24-hour long-acting $beta_2$-agonist (LABA) for COPD. Boehringer Ingelheim marketed Spiriva (tiotropium) which was indicated for the maintenance treatment of COPD. Spiriva was also a powder inhalation to be used once daily.

Inter-company dialogue had failed to resolve the issues.

1 Claim 'Sustained strength that helps your patients with COPD meet the varied demands of daily life'

This claim appeared as a headline on the front page (page 1) of the leavepiece.

COMPLAINT

Boehringer Ingelheim alleged that 'strength' was too generalised a claim to substantiate. This was not a meaningful clinical indicator and did not help the prescriber judge when or how to use Onbrez. Breaches of Clauses 7.2, 7.4 and 7.10 were alleged.

RESPONSE

Novartis submitted that it was clear to any health professional that in the context of COPD, 'strength' indicated significant efficacy in terms of markers for lung function such as forced expiratory volume in one second (FEV_1) and the associated relevant improvements in patient symptoms and quality of life. In a number of large, double-blind, placebo controlled studies (INLIGHT-1, INLIGHT-2, INVOLVE, INHANCE) indacterol had repeatedly and consistently demonstrated improvements in FEV_1 in COPD patients and associated relevant improvements in symptoms and quality of life of such magnitude and duration as to be clinically significant – justifying the use of 'strength'. Novartis noted that this did not claim or imply superiority over any other therapy – but rather, significant clinically meaningful efficacy in a given disease state. Further, the claim 'Sustained strength' was supported by the evidence cited in the summary of product characteristics (SPC) which showed that indacterol provided bronchodilation which lasted for 24 hours and that this effect was sustained over 1 year of treatment.

Novartis, therefore, denied breaches of Clauses 7.2, 7.4 and 7.10.

PANEL RULING

The Panel noted that the front cover of the leavepiece was headed 'NEW Onbrez Breezhaler: the first 24 hour LABA for COPD' and featured the picture of a lion apparently leaping, full stretch, from an inhaler device. The headline above the picture was 'Sustained strength that helps your patients with COPD meet the varied demands of daily life'. The Panel considered that the unqualified use of the word 'strength' was misleading; there was no indication as to what, in that context, 'strength' meant. The Panel noted Novartis' submission that 'strength' related to significant clinically meaningful efficacy in a given disease state and in that regard considered that 'strength' could be applied to all medicines. The Panel queried Novartis' submission that in the context of COPD health professionals would equate 'strength' with efficacy in terms of markers for lung function. The Panel considered that the strong, unqualified claim was misleading and, in that regard, could not be substantiated. A breach of Clauses 7.2 and 7.4 was ruled. Further, the Panel considered that the unqualified use of the word 'strength' implied some special property which could not be substantiated. A breach of Clause 7.10 was ruled. The Panel did not consider that the unqualified use of 'strength' in the claim was such that it did not help prescribers judge when or how to

use Onbrez. No breach of Clause 7.2 was ruled.

2 Claim 'Sustained relief in COPD'

This claim appeared as the strapline below the Onbrez product logo on pages 1 and 6 of the leavepiece.

COMPLAINT

Boehringer Ingelheim submitted that relief from what was not made clear. Breaches of Clauses 7.2, 7.4 and 7.10 were alleged.

RESPONSE

Novartis submitted that in the context of COPD, it was clear to the health professional that 'sustained relief' was from symptoms. For patients with COPD, it was widely accepted that the most consistently troublesome symptom was shortness of breath. It was the primary symptom that had the greatest impact on patients' lives, limiting their exercise capacity and adversely affecting their quality of life. Indacterol had been shown to consistently provide COPD patients with sustained relief from breathlessness (as shown by improvements in the Transitional Dysponoea Index (TDI) scores and reduced need for rescue medication) and associated improvements in quality of life, which were statistically and clinically superior to placebo and sustained over 24 hours for the duration of therapy.

Novartis submitted that the strapline could be substantiated and supported by the clinical evidence. The company denied the alleged breaches of Clauses 7.2, 7.4 and 7.10.

PANEL RULING

The Panel noted that Onbrez was the first long-acting beta$_2$-agonist for COPD. Section 5.1 of the SPC stated that 'The 24-hour bronchodilator effect of Onbrez Breezhaler was maintained from the first dose throughout a one-year treatment period with no evidence of loss of efficacy'. The Panel noted that Onbrez was indicated for maintenance of bronchodilator treatment of airflow obstruction in adults with COPD. The Panel considered that shortness of breath, limiting exercise capacity and the ability to perform daily activities, would be a major presenting symptom of COPD. In that regard the Panel did not consider that the strapline 'Sustained relief in COPD' was misleading as alleged. No breach of Clause 7.2 was ruled. The Panel considered that the claim could be substantiated and did not exaggerate the medicine's properties. No breach of Clauses 7.4 and 7.10 were ruled.

3 Claim 'Rapid bronchodilation* within 5 minutes that lasts all day'

This claim appeared as the first in a list of five bullet points on the inside flap (page 5) of the leavepiece. The asterisk referred to a footnote which read 'Onbrez Breezhaler is not licensed for acute symptomatic relief'.

COMPLAINT

Boehringer Ingelheim alleged that the use of an asterisk and footnote to qualify the rapid 5 minute bronchodilation claim was not adequate and in breach of Clause 7.

RESPONSE

Novartis submitted that the claim 'Rapid bronchodilation within 5 minutes that lasts all day' was clearly supported by the statements in Section 5.1 of the Onbrez Breezhaler SPC which read 'There was a rapid onset of action within 5 minutes after inhalation …' and 'Onbrez Breezhaler, administered once a day at doses of 150 and 300 microgram consistently provided clinically significant improvements in lung function (as measured by the forced expiratory volume in one second, FEV_1) over 24 hours across a number of clinical pharmacodynamic and efficacy studies'. In addition, this was further supported by the once daily dosing schedule.

Clinical data from the INSURE and INTIME studies demonstrated that indacterol had a rapid onset of action, and the INLIGHT-1 study, along with the active comparator trials, all demonstrated that indacterol had a 24-hour duration of action. The claim was, therefore, appropriate, could be referenced and did not require qualification.

The statement 'Onbrez Breezhaler is not licensed for acute symptomatic relief' was not included to qualify the claim but for completeness and to avoid doubt as the product was indicated for maintenance bronchodilator treatment of airflow obstruction in adults with COPD; it was not indicated as an acute treatment. The additional wording was not a claim or 'selling point' of the product. It was, therefore, inappropriate to consider this as a breach under Clause 7.

PANEL RULING

The Panel noted that the claim 'Rapid bronchodilation within 5 minutes that lasts all day' was asterisked to the footnote 'Onbrez Breezhaler is not licensed for acute symptomatic relief'. The Panel further noted that the claim itself was referenced to Vogelmeier *et al* (2009) (INTIME study) and Feldman *et al* (2009) (INLIGHT– 1 study). Novartis had submitted that the INSURE study (Balint *et al* 2009) also supported the claim for a rapid onset of action.

The Panel noted that Section 5.1 of the SPC stated that there was a rapid onset of action within 5 minutes after inhalation. It was not clear from the SPC whether this was demonstrated each day when Onbrez was used for long-term therapy.

The INTIME study demonstrated that Onbrez had an onset of action within 5 minutes on the first day of dosing. The INLIGHT-1 study measured trough FEV_1 ie between 23 and 24 hours post-dose after 12 weeks of treatment but also measured FEV_1 at individual time points on day 1. The study authors concluded, inter alia, that Onbrez demonstrated a fast onset (within 5 minutes) of bronchodilation from the first dose. The INSURE study was a single dose study which showed that Onbrez significantly increased FEV_1 at 5 minutes post-dose.

The Panel noted that COPD was a chronic disease and, as such, patients would require long-term therapy. The Panel noted that studies had shown that rapid bronchodilation was observed with the first dose of Onbrez. Novartis had not submitted data to show that subsequent daily doses of Onbrez also produced rapid bronchodilation within 5 minutes. In any event the Panel questioned the relevance of promoting a short onset of action in a long-term therapy when that long-term therapy was not also indicated for acute use. The Panel considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code.

4 Claim 'Improvements in breathlessness at least as effective as salmeterol and tiotropium'

This claim appeared as the third in a list of five bullet points on the inside flap (page 5) of the leavepiece.

COMPLAINT

Boehringer Ingelheim noted that Section 5.1 of the Onbrez SPC, 'Symptomatic benefits', stated, inter alia, that 'The magnitude of response was generally greater than seen with active comparators'. However there was a reference to table 2 of the SPC which included the percentage of patients who achieved the minimal clinically important difference TDI (transition dyspnoea index) – 57% for indacterol and 57% for tiotropium. 'At least as effective', implied possible superiority (ref Case AUTH/2270/10/09). Boehringer Ingelheim thus alleged that this was misleading in breach of Clause 7.2 as it was an exaggeration.

Boehringer Ingelheim noted that no reference was made on this page of the leavepiece to the open label nature of the study design which was also necessary to understand the clinical data. This item did not provide enough information for the prescriber to make informed decisions regarding the clinical data. A breach of Clause 7.2 was alleged.

RESPONSE

Novartis stated that it had conducted a number of separate clinical studies relating to indacterol. The INHANCE study showed that 71% of patients receiving indacterol 300mcg and 62% of patients receiving indacterol 150mcg reached the minimal clinically important difference for TDI. The comparable figures for tiotropium and placebo were 57% and 47% respectively. The INLIGHT-2 study showed that 57% of patients given indacterol 150mcg, 54% of salmeterol patients and 45% of placebo patients reached the minimal clinically important difference for TDC. The INLIGHT-2 study did not compare indacterol with tiotropium. In order to compare indacterol 150mcg with tiotropium one would have to use the full data from the INHANCE study. Novartis noted that Boehringer Ingelheim had selected the tiotropium figure from the INHANCE study, but then used the indacterol 150mcg data from the INLIGHT-2 study where there was no tiotropium comparator arm. Novartis considered that this was an inappropriate and misleading comparison. With respect to 'at least as effective as', the INHANCE study demonstrated that indacterol 150mcg and 300mcg showed comparable efficacy to tiotropium, however, for some endpoints there were statistically significantly improvements for indacterol vs tiotropium. The statement 'at least as effective as' was therefore accurate and justifiable and Novartis denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim 'Improvements in breathlessness at least as effective as salmeterol and tiotropium' was referenced to Kornmann *et al* (2009) (INLIGHT-2 study) and Donohue *et al* (2010) (INHANCE study).

Kornmann *et al* compared the efficacy and safety of once-daily indacterol 150mcg (n=330) and twice-daily salmeterol 50mcg (n=333) in patients with moderate to severe COPD in a randomized, double-blind, placebo-controlled, parallel-group study. Trough FEV_1 at 12 weeks was 60ml higher with indacterol than salmeterol ($p<0.001$) and this statistically significant treatment difference was maintained at week 26. The Panel noted, however, that a 120ml difference had been preset as denoting a clinical difference. Although indacterol improved the week 12 transition dyspnea index by 0.55 over salmeterol ($p=0.015$), a difference of 1 was considered clinically important. Indacterol allowed significantly more rescue-free days over 26 weeks (60% vs 55% with salmeterol ($p<0.05$)). The authors concluded, inter alia, that once-daily indacterol was superior to twice-daily salmeterol in its 24 hour bronchodilator effect and improved other clinical outcomes more than salmeterol.

Donohue *et al* compared the efficacy of indacterol and tiotropium over 26 weeks. Patients with moderate to severe COPD were randomised to double-blind, once-daily indacterol 150mcg (n=416) or 300mcg (n=416) or tiotropium 18mcg once-daily (n=415). At week 12, trough FEV_1 was 40-50ml greater in the indacterol patients than the tiotropium patients and although statistically significant when tested for superiority and non-inferiority ($p\leq0.01$ and $p<0.001$ respectively) the difference was less than the prespecified minimum important clinical difference of 120ml. The effects of indacterol and tiotropium were maintained over the course of the study. With regard to the transition dyspnea index

the proportion of patients with a clinically important improvement from base line was statistically significantly greater in the indacterol 300mcg group compared to tiotropium patients at weeks 4, 8, 12 and 26. There was no statistically significant difference between the indacterol 150mcg group and the tiotropium group at any of these time points. With regard to the transition dyspnea index total score, a bar chart in Donohue *et al* showed that the difference between tiotropium and indacterol was in favour of indacterol but always less than the clinically important difference of 1.

Donohue *et al* noted that the design of the study might have favoured indacterol therapy given that the tiotropium arm was open whereas the indacterol arm was double-blind. Nonetheless the authors believed that the study strongly indicated that indacterol was at least as effective as tiotropium.

The Panel noted that Kornmann *et al* had not shown a clinically significant difference in terms of trough FEV_1 and the transition dyspnea index between indacterol and salmeterol. There was a statistically significant advantage for indacterol with regard to rescue-free days. Similarly, Donohue *et al* had failed to show a clinically significant difference between indacterol and tiotropium in terms of trough FEV_1 and transition dyspnea index.

The Panel did not consider that the claim at issue reflected the balance of the evidence. The claim implied possible clinical superiority for indacterol whereas in terms of trough FEV_1 and the transition dyspnea index, the medicine had only been shown to be clinically similar to salmeterol and tiotropium. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

The Panel further considered that the claim was insufficiently complete such as to enable a prescriber to make an informed decision regarding the clinical data. A further breach of Clause 7.2 was ruled.

5 Claim 'Significantly more patients experienced clinically meaningful improvements in quality of life vs. other bronchodilators'

This claim appeared as the fourth in a list of five bullet points on the inside flap (page 5) of the leavepiece.

COMPLAINT

Boehringer Ingelheim noted that page 5 did not refer to the open label nature of the study design which was necessary to understand the clinical data. The leavepiece did not provide enough information for the prescriber to make informed decisions regarding the clinical data in breach of Clause 7.2.

RESPONSE

Novartis submitted that the claims on page 5 summarized the key messages for Onbrez Breezhaler. It was clear from the graph on the opposite page (page 2) in the leavepiece illustrating the comparison of indacterol with tiotropium and placebo in the INHANCE study that the tiotropium arm of this study was, indeed, open-label. This was stated twice on page 2. Novartis therefore denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim on page 5 was referenced to Kornmann *et al* (IN-LIGHT 2 study) and Yorgancioglu *et al* (2009) (INHANCE study).

Kornmann *et al* compared indacterol and salmeterol and reported that indacterol-treated patients had an improved health status with a 2.1 unit difference over salmeterol ($p<0.05$) at week 12. This difference, however, although statistically significant was less than the minimum clinically important difference of 4 points. There was no difference between the two products at week 26.

Yorgancioglu *et al* compared indacterol 150mcg and 300mcg and tiotropium 18mg all given once daily. The tiotropium was administered under open-label conditions. In terms of the percentage of patients achieving a clinically important difference of ≥4 units vs placebo in a health related quality of life score, there was a statistically significant difference between tiotropium and both doses of indacterol at weeks 4 and 8 in favour of indacterol; there was no difference between the medicines at week 12 and at week 26 there was only a statistically significant advantage for the lower dose of indacterol vs tiotropium.

The Panel considered that the claim at issue did not provide enough information about the clinical data as alleged. The Panel did not accept that the fact that page 2 of the leavepiece stated that the tiotropium study was open-label was sufficient as submitted by Novartis. A breach of Clause 7.2 was ruled.

6 Claim 'Onbrez Breezhaler: improvements in quality of life in more patients than salmeterol or tiotropium'

This claim appeared as the headline on the inside front page (page 2) which featured a bar chart depicting the results of Yorgancioglu *et al*. The claim was referenced to Kornmann *et al* and Yorgancioglu *et al*.

COMPLAINT

Boehringer Ingelheim submitted that the quality of life (QoL) outcomes, as reported by the St Georges Respiratory Questionnaire (SGRQ), were reported as secondary outcome measures at weeks 4, 8, 12 and 26 in Yorgancioglu *et al*, published in poster form at the 2009 European Respiratory Society (ERS) meeting.

Boehringer Ingelheim noted that Novartis had reported the improvements in QoL vs tiotropium at 26 weeks. This was 'cherry-picking' the data. Whilst there were differences in QoL between the indacterol and the tiotropium groups these were small and inconsistent. At weeks 4, 8 and 26 there was a significant improvement in the indacterol group compared with the tiotropium group. However, at 12 weeks there was no significant difference in QoL between the groups. Boehringer Ingelheim alleged a breach of Clause 7.2.

RESPONSE

Novartis submitted that the data for tiotropium was presented at 6 months as this was when tiotropium had been shown to reach its maximal effect in COPD patients (as evidenced by the peak in FEV_1 at 6 months in the UPLIFT trial (Tashkin *et al* 2008). Novartis therefore considered that a comparison at 6 months was the fairer option and of greater relevance to clinicians. Although there was no significant difference between indacterol and tiotropium at week 12, a statistically significant difference was observed between these arms of the study at all other time points (weeks 4, 8 and 26). The fact that the results showed a difference in three out of four of the time points (2 before [at weeks 4 and 8] and 1 after the 12 week point [at week 26]) suggested that there was a good degree of consistency. It would indeed be 'cherry-picking' to suggest that the 12 week value (no difference) was the most representative time point of the study as Boehringer Ingelheim seemed to imply. Novartis denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim was referenced to Kornmann *et al* and Yorgancioglu *et al* as in point 5 above. Kornmann *et al* reported that at week 12 the percentage of patients who achieved a clinically important improvement in a quality of life score (≥4 units) was highest in the indacterol group (57.9%) compared with salmeterol (46.8%) and placebo (39.1%) groups. The odds ratio for indacterol vs salmeterol was 1.59, p=0.009.

The claim headed a page which featured a bar chart which depicted the results at 26 weeks of Yorgancioglu *et al*. The bar chart showed that at week 26, 47.3% of patients treated with tiotropium had a clinically significant improvement in a quality of life measurement (SGRQ) vs 57.8% in the indacterol 150mcg treated group (p<0.01). There was, however, no significant difference between the percentage of patients achieving a clinically important improvement in the indacterol 300mcg treated group (52.5%) vs the tiotropium group (47.3%).

Yorgancioglu *et al* had shown that at weeks 4, 8 and 26, a statistically significantly greater percentage of patients on indacterol 150mcg achieved a clinically important difference in quality of life (≥4 units) vs tiotropium-treated patients (p<0.01). Only at week 12 was there no statistically significant difference between the two treatment groups. The Panel noted therefore, that in three out of the four time points measured there had been a statistically significant advantage for indacterol 150mcg vs tiotropium. The Panel further noted Novartis' submission that tiotropium reached its maximal effect in 6 months as evidenced by a peak in FEV_1. The Panel thus did not consider that to show the 26 week data was 'cherry picking' as alleged. No breach of Clause 7.2 was ruled.

7 Instructions for use

Page 3 of the leavepiece (the centre panel when opened out) featured five small drawings each showing a different step in the correct use of the Breezhaler device.

COMPLAINT

Boehringer Ingelheim alleged that the diagrams, which were an abridged version of the instructions for use found in the patient information leaflet (PIL) and the SPC implied that the process for use was simpler than it actually was. This was misleading and could cause misunderstandings between patients and prescribers: prescribers might not understand why a patient experienced difficulty with the instructions because they did not appreciate that it was necessary to work through a 13 step process. Boehringer Ingelheim alleged a breach of Clause 7.2.

RESPONSE

Novartis submitted that the 5-step instructions for use were intended to illustrate the mechanism of action of the Breezhaler device and were not a replacement for the full instructions in the PIL and the SPC. Health professionals seen by a Novartis representative would also receive a copy of the SPC and therefore full instructions on inhaler use. Novartis noted that the leavepiece had been reviewed by the MHRA as part of the pre-vetting of all marketing materials at launch. If Boehringer Ingelheim's concerns raised on the apparent basis of protecting patient safety had any merit, the MHRA would not have approved the piece. Novartis denied the alleged breach of Clause 7.2.

PANEL RULING

The Panel noted that the instructions for use had been given in an abbreviated form in the leavepiece; 5 steps had been illustrated compared with the 13 shown in the SPC. The Panel considered that although more instructions would have been helpful, the 5 steps shown were not misleading per se. No breach of Clause 7.2 was ruled.

Complaint received **11 October 2010**

Case completed **15 February 2011**