CASE AUTH/2843/4/16

# ANONYMOUS, NON CONTACTABLE v BOEHRINGER INGELHEIM

## Promotion of Spiriva

**An anonymous, non contactable complainant complained about the promotion of long-acting beta agonist/long-acting muscarinic antagonists (LABA/LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant referred to the first medicine to be licensed within this class, Ultibro Breezhaler (indacaterol maleate and glycopyrronium bromide), noting that it was clear from its European Public Assessment Report (EPAR) that the Committee for Medicinal Products for Human Use (CHMP) turned down an application that included its use to reduce COPD exacerbations because its effects, in that regard, were too small to recommend such use. Ultibro Breezhaler was subsequently licensed only as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD and thus its promotion in relation to COPD exacerbation reduction was off-label. The complainant cited other examples of what could be considered to be off-label promotion based on the CHMP ruling on LABA/LAMA combination inhaler indications and stated that additionally some LAMA inhaler products also involved off-label promotion. With regard to the latter the complainant drew attention to, *inter alia*, Boehringer Ingelheim's product, Spiriva (tiotropium).**

**Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD.**

**In relation to this case the complainant noted in particular a Spiriva journal advertisement which stated, 'With a long-term record of success in reducing symptoms, exacerbations and hospitalisations vs placebo ...'.**

**The complainant stated that Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD ie identical to Ultibro Breezhaler and the advertisement did not contain any other information warning of the off-label aspects to the promoted use of the product.**

**The complainant stated that his/her colleagues had little awareness that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these medicines in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had not clearly communicated the off-label nature of this use. The complainant stated that materials for the various inhalers to which he/she had drawn attention were probably just the tip of the iceberg. The complainant knew of numerous educational meetings/symposia with external speakers where exacerbation reduction data had been presented as part of product promotion.**

**A potential major concern for the complainant and his/her prescribing colleagues was that they might have unknowingly prescribed the above mentioned medicines to numerous COPD patients assuming that they were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if COPD patients subsequently suffered exacerbations unexpectedly because their prescribed LABA/LAMA combination inhalers might not be effective enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.**

**The detailed response from Boehringer Ingelheim is given below.**

**The Panel noted that Section 5.1 of the Spiriva summary of product characteristics (SPC) referred to its positive impact on exacerbations of COPD. The Panel noted that Section 1.1 of the National Institute for Health and Clinical Excellence (NICE) Guideline on the management of COPD listed the symptoms of the disease which were, *inter alia*, exertional breathlessness, chronic cough, regular sputum production and wheeze. In Section 1.3 the exacerbation of COPD was described as a sustained worsening of the patient's symptoms from their usual stable state which was beyond normal day-to-day variations and was acute in onset. The Global Initiative on Obstructive Lung Disease (GOLD) guidance similarly differentiated COPD symptoms and exacerbations. In the Panel's view, there was a difference between COPD symptoms and exacerbation of COPD although it accepted that patients with well controlled symptoms might be less likely to experience an exacerbation than patients with poorly controlled symptoms. In that regard the Panel considered that exacerbations might be referred to in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, reference to reduced COPD exacerbation must be set within the context of product's licensed indication and thus the primary reason to prescribe ie maintenance therapy to relieve symptoms.**

**The Panel noted that the advertisement included the claim, 'With a long-term record of success in reducing symptoms, exacerbations and hospitalisations vs placebo, Spiriva is a LAMA you can count on to help lead your COPD patients to everyday victories.' The Panel considered that the claim did not differentiate between the licensed**

**indication (reduction of symptoms) and the benefit of therapy (reduction of exacerbations). Other than in the prescribing information, the advertisement did not refer to the licensed indication for Spiriva and make it clear that this was the primary reason to prescribe. Reduction in COPD exacerbations appeared to be as much a reason to prescribe as reduction in symptoms. In that regard the Panel considered that the claim was inconsistent with the particulars listed in the Spiriva SPC and misleading with regard to the licensed indication for Spiriva. Breaches of the Code were ruled including that high standards had not been maintained.**

**The Panel noted that Boehringer Ingelheim also provided a copy of a slide deck used to train representatives and also used with and by health professionals. A benefit shown for Spiriva with regard to exacerbations was detailed in three slides, and in the summary slide one of the outcomes of the study (Tashkin *et al* 2008) was listed as 'Reduced exacerbations' and further details were provided. The data was not presented as being a benefit of using Spiriva to relieve COPD symptoms. The licensed indication for Spiriva was only stated in the prescribing information on the last slide.**

**The Panel again considered that Spiriva would be perceived as a medicine to reduce COPD exacerbations given that such use had been presented as a reason to prescribe *per se* and not as a benefit of using the medicine for its licensed indication. Although the SPC discussed reduction of exacerbation data, the Panel, noting the product's licensed indication, nonetheless considered that the slide deck was inconsistent with the particulars listed in the SPC. Slides that implied that exacerbation reduction was a primary reason to prescribe Spiriva were misleading. Breaches of the Code were ruled. In the Panel's view the slide deck which was used to train representatives, presented the exacerbation data in such a way as to advocate a course of action that was likely to breach the Code. Breaches of the Code were ruled including that high standards had not been maintained.**

**The Panel noted its comments and rulings above but did not consider that the matters were such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.**

An anonymous, non contactable complainant complained about the promotion of long-acting beta agonist/long-acting muscarinic antagonists (LABA/LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant referred to the first medicine to be licensed within this class, Ultibro Breezhaler (indacaterol maleate and glycopyrronium bromide) and stated that although it was clear from its European Public Assessment Report (EPAR – dated 25 July 2013) that an application was originally submitted for the relief of COPD symptoms and the reduction of exacerbations, the Committee for Medicinal Products for Human Use (CHMP) subsequently stated the medicine's effects on reducing the rate of exacerbations were too small to recommend its use for such. Ultibro Breezhaler was eventually licensed as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The complainant stated that it could be concluded that Ultibro Breezhaler was not granted a licence at the time to recommend its use for reducing exacerbations and alleged, therefore, that promotion of Ultibro Breezhaler in relation to COPD exacerbation reduction was off-label. The complainant provided a number of other examples of what could be considered to be off-label promotion based on the CHMP decision about LABA/LAMA combination inhaler indications and stated that additionally some LAMA inhaler products also involved off-label promotion. With regard to the latter the complainant drew attention, *inter alia*, to Boehringer Ingelheim's product, Spiriva (tiotropium).

Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD.

**COMPLAINT**

In relation to this case the complainant drew particular attention to a Spiriva journal advertisement (ref UK/SPI-121330, Aug 2012) which stated, 'With a long-term record of success in reducing symptoms, exacerbations and hospitalisations vs placebo ...'.

The complainant stated that Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD ie identical to Ultibro Breezhaler and the advertisement did not contain any other information warning of the off-label aspects to the promoted use of the product.

The complainant stated having spoken to his/her peers it was evident that there was very little awareness amongst fellow colleagues that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these medicines in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had most likely missed an ethical obligation to also clearly communicate the off-label nature of this use, either in materials or as instructions to representatives. The complainant concluded that the materials for the various inhalers to which he/she had drawn attention were most probably just the tip of a large iceberg. The complainant was aware of numerous educational meetings/symposia involving external speakers where exacerbation reduction data had been discussed and presented as part of product promotion.

A potential major concern for the complainant and his/her prescribing colleagues was that unknowingly, they might have prescribed LABA/LAMA combination inhalers or LAMA inhalers to numerous COPD patients based on the assumption that they were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if treated COPD patients subsequently suffered exacerbations unexpectedly. This was because prescribing LABA/LAMA combination inhalers might not be effective

enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question actually contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.

When writing to Boehringer Ingelheim the Authority asked it to respond to Clauses 2, 3.2, 7.2, 9.1 and 15.9. The edition of the Code would be that relevant at the time the materials were used.

**RESPONSE**

Boehringer Ingelheim submitted that the journal advertisement at issue was produced in August 2012 and not used after August 2014. Boehringer Ingelheim noted that the claim that Spiriva HandiHaler had 'a long-term record of success in reducing symptoms, exacerbations, and hospitalisations vs placebo', was referenced to the Spiriva HandiHaler summary of product characteristics (SPC) and Tashkin *et al* (2008). With regard to Clauses 3.2 and 7.2, the Spiriva SPC stated that it was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD. Section 5.1 of the SPC gave the following additional details:

> 'In a randomized, double-blind, placebo controlled trial of 1,829 patients with moderate to very severe COPD, tiotropium bromide statistically significantly reduced the proportion of patients who experienced exacerbations of COPD (32.2% to 27.8%) and statistically significantly reduced the number of exacerbations by 19% (1.05 to 0.85 events per patient year of exposure). In addition, 7.0% of patients in the tiotropium bromide group and 9.5% of patients in the placebo group were hospitalized due to a COPD exacerbation (p=0.056). The number of hospitalizations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure)'.

The same section of the SPC also included data for exacerbation reduction, including hospitalisation, vs salmeterol:

> 'Compared with salmeterol, Spiriva increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; p<0.001). Spiriva also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; p<0.001)'.

Tashkin *et al* further supported the claim by showing a statistically significant reduction in symptoms (as measured by the St George's Respiratory Questionnaire) with tiotropium vs placebo throughout the four years of the trial. It showed that, vs placebo, 'tiotropium was associated with a reduction in the risks of exacerbations, related hospitalizations, and respiratory failure'. Boehringer Ingelheim further noted that Halpin *et al* (2016) cited numerous other trials from the years before the advertisement, which confirmed the effect of tiotropium on exacerbations. There was, therefore, supporting evidence for tiotropium's 'long-term record', both in terms of trial duration and the number of years of accumulated evidence.

Boehringer Ingelheim submitted that the information in the advertisement was accurate, fair and balanced. It was consistent with the Spiriva SPC, which included discussion of its effect on reduction of symptoms, exacerbations, and hospitalizations.

With regard to Clause 15.9, Boehringer Ingelheim submitted that as the complainant was anonymous and no specific details about representatives' activity were supplied it was difficult to offer a specific rebuttal. However, Boehringer Ingelheim provided field force training material in use at the time of the advertisement.

Given the above, Boehringer Ingelheim submitted that it had acted in full accordance with both the spirit and letter of the Code, and it denied breaches of Clauses 2, 3.2, 7.2, 9.1 and 15.9.

In response to a request for further information, Boehringer Ingelheim submitted that with regard to the general allegation that it had 'missed an ethical obligation to also clearly communicate the off-label nature of this [exacerbation prevention] use', it did not believe that the discussion of the role of Spiriva in exacerbation reduction was a recommendation for 'off-label' use nor was it inconsistent with the SPC. Boehringer Ingelheim provided evidence as follows:

1 The SPC stated that the indication for Spiriva HandiHaler was:

> 'As a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).'

To understand this licence statement fully, Boehringer Ingelheim clarified what symptoms of COPD were expected to be relieved by use of Spiriva. The company explained that COPD caused several key symptoms, as recognised by guidance created and accepted by clinicians ie the Global initiative for chronic Obstructive Lung Disease (GOLD – updated 2016) which stated:

> 'The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production that can be variable from day-to-day.'

These guidelines also recognised that exacerbations of COPD were understood as being a symptomatic phenomenon of COPD:

> 'An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.'

Boehringer Ingelheim noted that the GOLD guidance additionally advised that prescription of long-acting bronchodilators (such as tiotropium) was an appropriate part of management strategy to reduce exacerbations:

> 'COPD exacerbations can often be prevented. Smoking cessation, influenza and pneumococcal vaccines, knowledge of current therapy including inhaler technique, and treatment with long-acting inhaled bronchodilators, with or without inhaled corticosteroids, and possibly phosphodiesterase-4 inhibitors, are all therapies that reduce the number of exacerbations and hospitalizations.'

2 A similar symptom-based definition of 'exacerbation' in the context of COPD was used by the National Institute for Health and Care Excellence (NICE) (clinical Guideline 101 (2010)) which stated:

> 'A rapid and sustained worsening of symptoms beyond normal day-to-day variations.'

The NICE guidance additionally mentioned numerous settings where addition of a long-acting muscarinic antagonist such as tiotropium would be appropriate for reduction of exacerbation risk:

> '1.2.2.5: Offer once-daily long-acting muscarinic antagonist (LAMA) in preference to four-times-daily short-acting muscarinic antagonist (SAMA) to people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required.'
>
> '1.2.2.6: In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy:
> If [forced expiratory volume over 1 second] FEV1 ≥ 50% predicted: either long-acting beta2 agonist (LABA) or LAMA if FEV1 < 50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA.'
>
> '1.2.2.7: In people with stable COPD and an FEV1 ≥ 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA:
> consider LABA+ICS in a combination inhaler
> consider LAMA in addition to LABA where ICS is declined or not tolerated.'
>
> '1.2.2.8: Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV1.'

Boehringer Ingelheim submitted that when clinicians prescribed a medicine for COPD, they therefore included reduction of exacerbations as an accepted element of management of symptoms. This approach was validated by national and international guidelines, and was consistent with the defined indication in Spiriva's SPC.

3 The SPC gave details of trial data for Spiriva related to exacerbations, compared with placebo and with the higher bar of an active comparator. Against placebo, the SPC stated:

> 'In a randomized, double-blind, placebo controlled trial of 1,829 patients with moderate to very severe COPD, tiotropium bromide statistically significantly reduced the proportion of patients who experienced exacerbations of COPD (32.2% to 27.8%) and statistically significantly reduced the number of exacerbations by 19% (1.05 to 0.85 events per patient year of exposure). In addition, 7.0% of patients in the tiotropium bromide group and 9.5% of patients in the placebo group were hospitalized due to a COPD exacerbation (p=0.056). The number of hospitalizations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure).'

Against salmeterol, the SPC gave further details of Spiriva's exacerbation data involving a large number of patients:

> 'A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram of SPIRIVA once daily with that of 50 microgram of salmeterol HFA pMDI twice daily on the incidence of moderate and severe exacerbations in 7,376 patients with COPD and a history of exacerbations in the preceding year.

A table summarising the exacerbation endpoints was provided. Compared with salmeterol, SPIRIVA increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001). SPIRIVA also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).'

In summary, Boehringer Ingelheim submitted that discussion of the use of Spiriva in exacerbation reduction was in keeping with the licence statement, in keeping with the data and content of the SPC, in keeping with use by clinicians and appropriately reflected in the recommendations of national and international guidelines. The product had not been promoted since 2014.

**PANEL RULING**

The Panel noted that Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms in patients with COPD. Section 5.1 of the SPC referred to its positive impact on exacerbations of COPD. The Panel noted that Section 1.1 of the NICE Guideline on the management of COPD listed the symptoms of the disease which were, *inter alia*, exertional breathlessness, chronic cough, regular sputum production and wheeze. In Section 1.3 of the Guideline, the exacerbation of COPD was described as a sustained worsening of the patient's symptoms

from their usual stable state which was beyond normal day-to-day variations and was acute in onset. The GOLD guidance similarly differentiated COPD symptoms and exacerbations. In the Panel's view, there was a difference between COPD symptoms and exacerbation of COPD although it accepted that patients whose symptoms were well controlled might be less likely to experience an exacerbation of their condition than patients with poorly controlled symptoms. In that regard the Panel considered that reference to exacerbations might be included in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, any reference to reduced COPD exacerbation must be set within the context of product's licensed indication and thus the primary reason to prescribe ie maintenance therapy to relieve symptoms.

The Panel noted that Boehringer Ingelheim had been asked to consider the requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 and advised that the edition of the Code that would be relevant would be that which was in force when the materials were used. The Panel considered, however, that given the matters at issue, the relevant substantial requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 had not changed since the 2012 Code (the earliest Code relevant to the material at issue) and so all of the rulings below are made under the 2016 Code.

The Panel noted that the advertisement included the claim, 'With a long-term record of success in reducing symptoms, exacerbations and hospitalisations vs placebo, Spiriva is a LAMA you can count on to help lead your COPD patients to everyday victories.' The Panel considered that the claim did not differentiate between the licensed indication (reduction of symptoms) and the benefit of therapy (reduction of exacerbations). Other than in the prescribing information, the advertisement did not refer to the licensed indication for Spiriva and make it clear that this was the primary reason to prescribe. Reduction in COPD exacerbations appeared to be as much a reason to prescribe as reduction in symptoms. In that regard the Panel considered that the claim was inconsistent with the particulars listed in the Spiriva SPC. A breach of Clause 3.2 was ruled. The claim was misleading with regard to the licensed indication for Spiriva; a breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that Boehringer Ingelheim also provided a copy of a slide deck to be used to train representatives but also to be used with and by health professionals (ref UK/SPI-131788, February 2014) which post-dated the advertisement by 18 months. The slide deck detailed Tashkin *et al* (cited in the advertisement) which assessed whether Spiriva was associated with a decrease in the rate of decline of FEV1 over time in COPD patients who either had Spiriva or placebo added to their usual respiratory medicines. A benefit was shown for Spiriva with regard to exacerbations (a secondary objective of the trial) and this was detailed in three slides, and in the summary slide one of the outcomes of the study was listed as 'Reduced exacerbations' and further details were provided. The data was not presented as being a benefit of using Spiriva to relieve COPD symptoms. The licensed indication for Spiriva was only stated within the prescribing information on the last slide.

The Panel again considered that Spiriva would be perceived as a medicine to reduce COPD exacerbations given that such use had been presented as a reason to prescribe *per se* and not as a benefit of using the medicine for its licensed indication. Although the SPC did discuss reduction of exacerbation data, the Panel, noting the product's licensed indication, nonetheless considered that the slide deck was inconsistent with the particulars listed in the SPC. A breach of Clause 3.2 was ruled. Slides that implied that exacerbation reduction was a primary reason to prescribe Spiriva were misleading. A breach of Clause 7.2 was ruled. In the Panel's view the slide deck which was used to train representatives, presented the exacerbation data in such a way as to advocate a course of action that was likely to breach the Code. A breach of Clause 15.9 was ruled. In the Panel's view, high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such. The Panel noted its comments and rulings above but did not consider that the matters were such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

**Complaint received** **25 April 2016**

**Case completed** **16 September 2016**