CASES AUTH/2840/4/16 and AUTH/2847/5/16

ANONYMOUS, NON CONTACTABLE v NOVARTIS and PFIZER

Promotion of Ultibro Breezhaler and Seebri Breezhaler

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 noted that the medicines were licensed for the relief of COPD symptoms but appeared to have been additionally promoted to reduce exacerbations. The complainant stated that some LAMA inhalers had also similarly been promoted off-label. The complainant drew attention to, *inter alia*, Ultibro Breezhaler (indacaterol (LABA)/glycopyrronium (LAMA)) and Seebri Breezhaler (glycopyrronium (LAMA)) both co marketed by Novartis Pharmaceuticals UK and Pfizer.

Ultibro Breezhaler and Seebri Breezhaler were both indicated as maintenance bronchodilator treatments to relieve symptoms in adults with COPD.

The complainant noted that the first LABA/LAMA fixed combination to be licensed was Ultibro Breezhaler and stated 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 exacerbations, because its effects on such 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. In relation to this case the complainant drew attention to a journal advertisement which stated that 'Ultibro Breezhaler can significantly reduce your patients' rate of moderate to severe exacerbations'. Similarly, the complainant alleged that a leavepiece contained an off-label claim for Seebri Breezhaler namely, '... significantly reduces the risk of first moderate/severe COPD exacerbation by 31%'. Neither contained any other information warning of the off-label aspects to the promoted use of the products.

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 the materials for the various inhalers to which he/she had drawn attention were most probably just the tip of the iceberg; he/she 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 LABA/LAMA combination inhalers or LAMA inhalers 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 Novartis and Pfizer is given below.

The Panel noted that both products were indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD. Section 5.1 of the respective Ultibro Breezhaler and Seebri Breezhaler summaries of product characteristics (SPCs) referred to each medicine's 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 wheezing. 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 for Chronic 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 the primary reason to prescribe ie maintenance therapy to relieve symptoms.

The Panel noted that the Ultibro Breezhaler advertisement at issue included the sub-heading 'Ultibro Breezhaler offers benefits beyond

current standard COPD maintenance therapies' beneath which were four claims one of which was 'vs salmeterol/fluticasone Ultibro Breezhaler can significantly reduce your patients' rate of moderate or severe exacerbations', referenced to Zhong *et al* (2015), the LANTERN study. In that regard the Panel considered that the claim for a benefit vs salmeterol/fluticasone appeared to be a consequence of using Ultibro Breezhaler as a maintenance therapy and not the reason to prescribe *per se,* as alleged. Given the context in which it appeared, the claim was not misleading with regard to the licensed indication for Ultibro Breezhaler. No breaches of the Code were ruled including that high standards had been maintained.

These rulings also applied to the 'Wealth of data' leavepiece and on balance to the sales aid. No breaches of the Code were ruled.

Novartis also provided a copy of a leavepiece, 'What is the right treatment choice for your patients?'. Under a heading of 'Ultibro Breezhaler offers patients effective relief from symptoms of COPD at a price of £32.50' was boxed text entitled 'Reduces exacerbation risk beyond tiotropium (open label) and [salmeterol/fluticasone]' which reported the results from Zhong *et al*. The leavepiece, however, did not clearly state that Ultibro Breezhaler was a maintenance therapy to relieve COPD symptoms such that the boxed text would be read within the context of the licensed indication. In the Panel's view the leavepiece implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction in exacerbations being a benefit of using the medicine as maintenance therapy. In the Panel's view the leavepiece was inconsistent with the particulars listed in the Ultibro Breezhaler SPC; it misleadingly implied that exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler. Breaches of the Code were ruled including that high standards had not been maintained.

A speaker slide deck, 'Evolving science; Dual bronchodilation', examined the burden of COPD and the challenges of treatment and included an overview of clinical studies for, *inter alia,* Ultibro Breezhaler. The slide which introduced Ultibro Breezhaler (slide 54) clearly stated that it was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. A subsequent section on exacerbations referred to the positive data from the SPARK (vs glycopyrronium and tiotropium) and LANTERN (vs salmeterol/fluticasone (LABA/inhaled corticosteroid (ICS)) studies. Slide 80 within a subsequent section on health-related quality of life, was headed 'Summary: Ultibro Breezhaler significantly improved important patient outcomes vs monotherapies and LABA/ICS' and in that regard listed exacerbations. The second bullet point of the final concluding slide (slide 101) stated 'Once daily Ultibro Breezhaler demonstrated superior efficacy compared with placebo, its monocomponents indacaterol and glycopyrronium, the current standard of care (tiotropium) and LABA/ICS'. It was not stated what the superior efficacy related to. In the Panel's view, given the length of the slide deck and the number of topics discussed, it was possible that, after 101 slides, some viewers would have forgotten exactly what Ultibro Breezhaler was indicated for; some viewers might be left with the impression that Ultibro Breezhaler could be prescribed for the reduction of exacerbations *per se* which was not consistent with the particulars listed in its SPC. That the presentation implied that Ultibro Breezhaler could be used to reduce COPD exacerbations and was a primary reason to prescribe the product was misleading. Breaches of the Code were ruled including that high standards had not been maintained.

The Panel considered that the training course presentation could have benefitted from a more explicit statement as to the licensed indication for Ultibro Breezhaler and that any reduction in exacerbations was to be discussed as a benefit of maintenance therapy and not as a reason to prescribe *per se*. Nonetheless, on balance, the Panel did not consider that the material encouraged representatives to promote Ultibro Breezhaler for exacerbation reduction. No breaches were ruled.

The Panel noted that the Seebri Breezhaler leavepiece at issue stated on the front cover that the medicine was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. Page 2 of the leavepiece described a typical patient and stated that he 'wants a treatment that will help him breathe better in the morning…and throughout the day'. Page 3 of the leavepiece included the claim that, compared with placebo, Seebri Breezhaler 'Significantly reduces the risk of first moderate/severe COPD exacerbation by 31% (p=0.023)'. The Panel did not consider that the leavepiece promoted Seebri Breezhaler for the reduction of COPD exacerbation as alleged. Preceding claims largely discussed symptom control. The reference to exacerbations had been presented within the context of the licensed indication ie as a benefit of maintenance therapy and not the reason to prescribe *per se*. The Panel considered that the promotion of Seebri Breezhaler had been consistent with the particulars listed in the SPC. The leavepiece did not imply that exacerbation reduction was a primary reason to prescribe Seebri Breezhaler and so was not misleading in that regard. No breaches of the Code were ruled including that high standards had been maintained.

In response to the complainant's wider concerns about the promotion of Seebri Breezhaler, Novartis provided a copy of two internal training presentation. Overall the Panel considered that the presentations suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated; both were ruled in breach of the Code including that high standards had not been maintained.

The Seebri Breezhaler sales aid contained a page which was headed 'How can you help delay the time to first moderate to severe COPD exacerbation for your patients' which appeared above a graph comparing the effect of Seebri Breezhaler with that of placebo. The claim at the bottom of the slide read

'Initiate Seebri Breezhaler to reduce your patients' risk of exacerbations'. Finally the Panel noted that although a set of Seebri Breezhaler speaker slides only briefly referred to the positive exacerbation data from Kerwin *et al* (2012) compared with placebo, those results were not put into context by any statement of the licensed indication for the medicine. The Panel considered that the sales aid and the speaker slides both suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated; this was inconsistent with the particulars listed in the Seebri Breezhaler SPC. The materials implied that exacerbation reduction was a primary reason to prescribe Seebri Breezhaler. Breaches of the Code were ruled including that high standards had not been maintained.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its rulings and comments above but considered that the matters were not such as to bring discredit upon, or reduce confidence in, the 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 fact that the medicines were licensed for the relief of COPD symptoms but appeared to have been additionally promoted to reduce exacerbations. The complainant stated that some LAMA inhalers had also similarly been promoted off-label. The complainant drew attention, *inter alia*, to Ultibro Breezhaler (indacaterol (LABA)/glycopyrronium (LAMA)) and Seebri Breezhaler (glycopyrronium (LAMA)) both co marketed by Novartis Pharmaceuticals UK Ltd and Pfizer Limited.

Ultibro Breezhaler and Seebri Breezhaler were both indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD.

COMPLAINT

The complainant noted that the first LABA/LAMA fixed combination to be licensed was Ultibro Breezhaler 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. In relation to this case the complainant drew attention to a journal advertisement (ref UK/ULT/16-0028b (1) – February 2016) which stated that 'Ultibro Breezhaler can significantly reduce your patients' rate of moderate to severe exacerbations'.

Similarly, the complainant alleged that a leavepiece (ref SBR0003 – September 2014) contained an off-label claim for Seebri Breezhaler namely, '... significantly reduces the risk of first moderate/severe COPD exacerbation by 31%'.

Neither of the two items mentioned above contained any other information warning of the off-label aspects to the promoted use of the products.

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 products 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 instruction 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 the products 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.

In writing to Novartis and Pfizer the Authority asked them 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

Novartis noted that Ultibro Breezhaler was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD and denied that the claim 'Ultibro Breezhaler can significantly reduce your patients'

rate of moderate to severe exacerbations' constituted the off-label promotion because:

- The indication included symptomatic COPD patients regardless of exacerbation history or risk.
- Statistically significant reductions in the annualised rate of moderate to severe exacerbations and all COPD exacerbations (mild, moderate or severe) were described within Section 5.1 of the Ultibro Breezhaler summary of product characteristics (SPC). Statements regarding statistically significant reductions in the rate of exacerbations were therefore consistent with the particulars of the SPC.
- Two randomised controlled clinical trials had demonstrated significant reductions in exacerbations and so there was clinical evidence to substantiate the information. In the SPARK study (Wedzicha *et al* 2013), Ultibro Breezhaler statistically significantly reduced the annualised rate of moderate or severe COPD exacerbations by 12% compared with glycopyrronium ($p = 0.038$) and all COPD exacerbations (mild, moderate or severe) by 15% compared to glycopyrronium ($p = 0.001$). In addition, the LANTERN study (Zhong *et al* 2015) demonstrated a statistically significant 31% reduction in moderate to severe exacerbations for Ultibro Breezhaler vs salmeterol/fluticasone.

Furthermore, the complainant's example was only a component of the advertisement which was fully referenced and contained appropriate Code related requirements including (and not limited to) the prescribing information which clearly stated the licensed indication. Therefore, for all the reasons above, Novartis denied the complainant's allegation that the claim, 'Ultibro Breezhaler can significantly reduce your patients' rate of moderate to severe exacerbations', was off-label promotion.

In summary, Novartis submitted that the claim complied with the requirements of Clause 3.2, as it was in accordance with the terms of the Ultibro Breezhaler marketing authorisation and was consistent with the particulars and benefits described in its SPC. Novartis also submitted that the claim complied with Clause 7.2 in that the information was accurate, balanced, fair, objective and unambiguous and was based on an up-to-date evaluation of all the evidence available when the advertisement was published. Hence it would not mislead readers either directly or by implication, by distortion, exaggeration or undue emphasis.

With regards to compliance with Clause 15.9, Novartis did not believe it was relevant to this material. The item in question was an advertisement in a health professional journal. No representative briefing was required.

Novartis submitted that high standards had been maintained and that the Ultibro Breezhaler advertisement complied with the Code. Novartis denied a breach of Clause 9.1 and further denied that the material had brought the industry into disrepute, in breach of Clause 2.

Turning to the Seebri Breezhaler leavepiece, Novartis noted that it was indicated for maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Novartis did not consider that the claim that Seebri Breezhaler 'significantly reduces the risk of first moderate/severe COPD exacerbation by 31%' constituted off-label promotion because:

- The indication included symptomatic COPD patients regardless of exacerbation history or risk.
- Statistically significantly prolonged time to first moderate or severe exacerbation and reduction in the rate of moderate or severe COPD exacerbations (0.53 exacerbations/year vs 0.77 exacerbations/year, ($p < 0.001$)) were described within Section 5.1 of the Seebri Breezhaler SPC. Statements regarding statistically significant reductions in the rate of exacerbations were therefore consistent with the particulars of the SPC.
- The claim was supported by evidence from a randomised clinical trial which demonstrated a statistically significant 31% reduction in the risk of COPD exacerbations in terms of time to first moderate or severe COPD exacerbation compared with placebo (hazard ratio [HR] 0.69, 95% CI 0.500-0.949; ($p = 0.023$)) (D'Urzo *et al* 2011) which was cited in the leavepiece.

Furthermore the complainant's cited example was only a component of the leavepiece which was fully referenced and contained appropriate Code related requirements including (and not limited to) the prescribing information which clearly stated the licensed indication. Therefore, for all the reasons above, Novartis denied the complainant's allegation that the statement was off-label promotion.

In summary, Novartis submitted that the claim at issue, '... significantly reduces the risk of first moderate/severe COPD exacerbation by 31%', within the Seebri Breezhaler promotional material complied with Clause 3.2 as it was in accordance with the terms of the medicine's marketing authorization and was consistent with the particulars and benefits described in the Seebri Breezhaler SPC. Novartis further submitted that the claim complied with Clause 7.2 in that the information was accurate, balanced, fair, objective and unambiguous and was based on an up-to-date evaluation of all the evidence available when the leavepiece was used. Hence it would not mislead a reader either directly or by implication, by distortion, exaggeration or undue emphasis.

With regard to compliance with Clause 15.9, the leavepiece was comprised of excerpts from the Seebri Breezhaler sales aid for which training was completed face-to-face at the Seebri Breezhaler launch meeting in September 2014. The leavepiece was subsequently made available for trained representatives to use.

Novartis submitted that high standards had been maintained and the information contained in the Seebri Breezhaler leavepiece complied with the Code. Novartis denied that this was in breach of

Clause 9.1 and further denied that the leavepiece had brought the industry into disrepute, in breach of Clause 2.

With regard to the role of the LAMA inhalers (eg Seebri Breezhaler), LABA/LAMA combination inhalers (eg Ultibro Breezhaler) and LABA/ICS combination inhalers and their use in preventing COPD exacerbations Novartis explained that the natural history of COPD included a degree of symptom burden (typically breathlessness, cough and sputum production) punctuated with episodes of worsening of these symptoms (referred to as exacerbations). An exacerbation was defined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines as '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'.

LAMAs, LABA/LAMA fixed dose combinations and LABA/inhaled corticosteroid (ICS) fixed dose combinations were all licensed for the symptomatic treatment of patients with COPD as illustrated by the following examples:

- Spiriva (tiotropium - a LAMA inhaler) was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD.

- Seebri Breezhaler (a LAMA inhaler) was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

- Ultibro Breezhaler (a LABA/LAMA combination inhaler) was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

- Seretide (salmeterol/fluticasone - a LABA/ICS combination inhaler) was indicated for the symptomatic treatment of patients with COPD, with a forced expiratory volume in 1 second (FEV1) < 60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who had significant symptoms despite regular bronchodilator therapy.

These medicine classes were recommended for use by the GOLD Guidelines and by the National Institute for Health and Care Excellence (NICE) therapeutic pathway for inhaled therapy for COPD in Clinical Guideline CG101. Recommendations were based on a patient's symptomatic response and preference, the medicine's adverse event profile and costs, as well as the potential to reduce exacerbations. LAMA and LABA/LAMA therapies were considered alternative options to LABA/ICS. Preference was not given to LABA/ICS by virtue of it containing an anti-inflammatory component (inhaled corticosteroid) and all treatment options had been shown to reduce exacerbations. The complainant was thus incorrect to suggest that there might be a concern in using LAMAs or LABA/LAMA combinations to reduce exacerbations because they did not contain an anti-inflammatory component. In fact, as described above, the LANTERN study demonstrated a statistically significant 31% reduction in moderate to severe exacerbations for Ultibro Breezhaler (LABA/LAMA) compared with salmeterol/fluticasone (LABA/ICS).

In summary Novartis submitted that its communications regarding the use of LAMA and LABA/LAMA combination treatment had been responsible, accurate, not misleading and based on an up-to-date evaluation of the latest clinical evidence. The data on reducing exacerbations for Ultibro Breezhaler and Seebri Breezhaler were substantiated and consistent with the particulars in their respective SPCs. Representatives were well-briefed on all promotional materials and high standards had been maintained at all times. The reputation of the industry had never been compromised. Novartis thus denied any breach of Clauses 3.2, 7.2, 15.9, 9.1 or 2 of the Code.

On receipt of Novartis' response, it became apparent that the medicines were co-promoted with Pfizer and the matter was taken up with Pfizer (Case AUTH/2847/5/16).

RESPONSE FROM PFIZER

Pfizer submitted that the initial response provided by Novartis was agreed by both Pfizer and Novartis as part of the Pfizer-Novartis Alliance and that any subsequent correspondence on the matter was to be considered as joint responses from both companies.

FURTHER INFORMATION FROM NOVARTIS

In response to a request for further information, Novartis submitted a copy of the relevant part of the training material covering exacerbations data for the Seebri Breezhaler sales aid.

Novartis submitted that a generally accepted definition of clinical practice guidelines was that they were systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. Published methods for development of valid guidelines differed in their detail but all were founded on the following three essential principles:

1 guidelines must be evidence based, with recommendations based on a systematic review, including critical appraisal, of published literature;

2 individual recommendations must be evidence-linked, using a recognised grading scheme that explicitly summarises the type and quality of evidence on which they were based; and

3 guideline development must be multidisciplinary, undertaken by a group in which all stakeholders, including patients or service users, for the clinical topic are represented.

Guidelines were usually produced at national or international level by medical associations or governmental bodies. Local healthcare providers might produce their own set of guidelines or adapt them from existing top-level guidelines. In developing local clinical guidelines, consideration would likely be given to issues such as local burden of disease,

the availability of effective and efficient healthcare interventions, evidence of variation in practice and evidence of current suboptimal performance.

While industry generated literature might be considered in the development of clinical guidelines, guidelines were independent, formal, evidence-based recommendations over which pharmaceutical companies had no editorial control.

Novartis disagreed with the complainant's assertion that the promotion of Ultibro Breezhaler and Seebri Breezhaler had most likely missed an ethical obligation.

Regarding the complainant's assertion of '… off-label nature of this use, …' Novartis refuted that statement and noted the approved indications for Ultibro Breezhaler and of Seebri Breezhaler in Section 4.1 (Therapeutic indications) of their respective SPCs, and also of the statements in Section 5.1 (Pharmacodynamic properties) about statistically significant reductions in exacerbation risk.

The GOLD 2016 Guidelines noted that the characteristic symptoms of COPD were chronic and progressive dyspnoea, cough, and sputum production that could be variable from day-to-day, and that an exacerbation of COPD was an acute event characterised by a worsening of the patient's respiratory symptoms that was beyond normal day-to-day variations, and led to a change in medication. An exacerbation was therefore part of the spectrum of symptomatology associated with COPD, and indeed, reduction of exacerbation risk in COPD was widely studied and widely reported.

Both Ultibro Breezhaler and Seebri Breezhaler were indicated as maintenance bronchodilator treatments to relieve symptoms in adults with COPD. The discussion of information and data included in Section 5.1 of each SPC specifically related to the patient population included in Section 4.1 of the same SPC and therefore did not constitute off-label promotion.

There were no restrictions in the Ultibro Breezhaler or Seebri Breezhaler indication in their respective SPCs regarding exacerbation history or risk, and therefore no reason why data relating to exacerbation risk reduction or other clinically relevant endpoints found in Section 5.1 should not be used in promotional materials.

Novartis provided copies of relevant current Ultibro Breezhaler and Seebri Breezhaler materials including presentations and representatives' briefing materials which referred to exacerbation reduction data.

PANEL RULING

The Panel noted that both Ultibro Breezhaler and Seebri Breezhaler were indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD. Section 5.1 of the respective SPCs referred to each medicine's 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 wheezing. 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 the primary reason to prescribe ie maintenance therapy to relieve symptoms.

The Panel noted that Novartis and Pfizer 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 2014 Code (the earliest Code relevant to the material at issue) and so all of the rulings below were made under the 2016 Code.

The Panel noted that the Ultibro Breezhaler advertisement at issue included the sub-heading 'Ultibro Breezhaler offers benefits beyond current standard COPD maintenance therapies' beneath which were four claims one of which was 'vs salmeterol/fluticasone Ultibro Breezhaler can significantly reduce your patients' rate of moderate or severe exacerbations' which was referenced to Zhong *et al*, the LANTERN study. In that regard the Panel considered that the claim for a benefit vs salmeterol/fluticasone appeared to be a consequence of using Ultibro Breezhaler as a maintenance therapy and not the reason to prescribe *per se*, as alleged. In that regard no breach of Clause 3.2 was ruled. Given the context in which it appeared, the claim was not misleading with regard to the licensed indication for Ultibro Breezhaler. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

In response to the complainant's wider concerns about the promotion of Ultibro Breezhaler, Novartis provided a copy of the Ultibro Breezhaler interactive sales aid (ref UK/ULT/15-0268b) which listed, in order, maintaining an active lifestyle, reducing breathlessness and reducing exacerbations as important when managing COPD patients. The Panel was concerned that it appeared that health professionals could choose only to learn about the reduction in exacerbations. The introductory slide to that section described exacerbation reduction as a priority of COPD management and detailed the consequences of exacerbations. The following slide

introduced the exacerbation data with the heading 'How can you control COPD symptoms while helping to reduce exacerbations?' This was followed by two slides headed 'Start a new chapter in improving symptoms' separated by a slide headed 'Start with a new chapter in reducing exacerbations'. All of the slides bore the product logo and a picture of the device. The Panel considered that this section of the sales aid was on the outer limits of acceptability and queried whether sufficient weight had been given to the licensed indication. That part of the exacerbations section which dealt with the comparison of Ultibro Breezhaler vs salmeterol/fluticasone, again reported the findings of Zhong *et al*.

A 'Wealth of data' leavepiece (ref UK/ULT/15-0270a) was headed on page 1 with 'If you have patients with COPD that are still symptomatic despite their maintenance therapy, there is something we'd like to bring to light …'. Page 3 was headed 'Ultibro Breezhaler offers benefits beyond current standard maintenance therapies' below which was a claim that, compared with tiotropium, Ultibro significantly reduced the rate of all exacerbations.

The Panel noted its comments and rulings above with regard to the Ultibro Breezhaler advertisement and considered that they applied to the 'Wealth of data' leavepiece and on balance to the sales aid. No breaches of Clause 3.2, 7.2 and 9.1 were ruled.

Novartis also provided a copy of a leavepiece (ref UK/ULT/15-0025) entitled 'What is the right treatment choice for your patients?'. Under a heading of 'Ultibro Breezhaler offers patients effective relief from symptoms of COPD at a price of £32.50' was boxed text entitled 'Reduces exacerbation risk beyond tiotropium (open label) and [salmeterol/fluticasone]' which reported the results from Zhong *et al* described above. The leavepiece, however, did not clearly state that Ultibro Breezhaler was a maintenance therapy to relieve COPD symptoms such that the boxed text would be read within the context of the licensed indication. In the Panel's view the leavepiece implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction in exacerbations being a benefit of using the medicine as maintenance therapy. In the Panel's view the leavepiece was inconsistent with the particulars listed in the Ultibro Breezhaler SPC and a breach of Clause 3.2 was ruled. The leavepiece implied that that exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

A speaker slide deck (ref UK/ULT/16-0025) entitled 'Evolving science; Dual bronchodilation' examined the burden of COPD and the challenges of treatment and included an overview of clinical studies for, *inter alia*, Ultibro Breezhaler. The slide which introduced Ultibro Breezhaler (slide 54) clearly stated that it was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. A subsequent section on exacerbations referred to the positive data from the SPARK (vs glycopyrronium and tiotropium) and LANTERN (vs salmeterol/fluticasone (LABA/ICS)) studies. Slide 80 within a subsequent section on health-related quality of life, was headed 'Summary: Ultibro Breezhaler significantly improved important patient outcomes vs monotherapies and LABA/ICS' and in that regard listed exacerbations. The second bullet point of the final concluding slide (slide 101) stated 'Once daily Ultibro Breezhaler demonstrated superior efficacy compared with placebo, its monocomponents indacaterol and glycopyrronium, the current standard of care (tiotropium) and LABA/ICS'. It was not stated what the superior efficacy related to. In the Panel's view, given the length of the slide deck and the number of topics discussed, it was possible that, after 101 slides, some viewers would have forgotten exactly what Ultibro Breezhaler was indicated for; some viewers might be left with the impression that Ultibro Breezhaler could be prescribed for the reduction of exacerbations *per se* which was not consistent with the particulars listed in its SPC. A breach of Clause 3.2 was ruled. That the presentation implied that Ultibro Breezhaler could be used to reduce COPD exacerbations and was a primary reason to prescribe the product was misleading and a breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Ultibro Breezhaler training course presentation (ref UK/ULT/15-0474) referred to COPD maintenance and that health professionals effectively control COPD symptoms through optimal bronchodilation as a cornerstone of COPD management. In a section entitled 'Ultibro Campaign Material "Benefits Beyond"', the structure of the sales aid as referred to above was discussed and a flow diagram included a box labelled 'Ultibro promise exacerbations'. Three subsequent slides discussed exacerbation data using the same slides as used in the sales aid. The Panel considered that the training presentation could have benefitted from a more explicit statement as to the licensed indication for Ultibro Breezhaler and that any reduction in exacerbations was to be discussed as a benefit of maintenance therapy and not as a reason to prescribe *per se*. Nonetheless, on balance, the Panel did not consider that the material encouraged representatives to promote Ultibro Breezhaler for exacerbation reduction. No breach of Clause 15.9 was ruled. The Panel considered that high standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel noted that the Seebri Breezhaler leavepiece (ref SBR0003) at issue stated on the front cover that the medicine was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. Although the statement was in small type, it was visually prominent given that it was in black print on a white background. Page 2 of the leavepiece described a typical patient and stated that he 'wants a treatment that will help him breathe better in the morning… and throughout the day'. Page 3 of the leavepiece included the claim that, compared with placebo, Seebri Breezhaler 'Significantly reduces the risk of first moderate/severe COPD exacerbation by 31% (p=0.023)'. The Panel did not consider that the leavepiece promoted Seebri Breezhaler for

the reduction of COPD exacerbation as alleged. Preceding claims largely discussed symptom control. The reference to exacerbations had been presented within the context of the licensed indication ie as a benefit of maintenance therapy and not the reason to prescribe *per se*. The Panel considered that the promotion of Seebri Breezhaler had been consistent with the particulars listed in the SPC. No breach of Clause 3.2 was ruled. The leavepiece did not imply that exacerbation reduction was a primary reason to prescribe Seebri Breezhaler and so was not misleading in that regard. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

In response to the complainant's wider concerns about the promotion of Seebri Breezhaler, Novartis provided a copy of an internal training presentation (ref SBR0023). In an overview of COPD it was stated reduced rate of exacerbations were key issues for payers and clinicians. In an overview of the brands, a slide on positioning Seebri Breezhaler indicated that it was to be 'First line LAMA for all your COPD patients'. The two key messages were 'Initiate Seebri Breezhaler to help your patients breathe more easily during the mornings…and throughout the day' and 'Reduces your patients risk of exacerbations'. The presentation included a slide which stated 'Important Seebri Breezhaler is licensed as a maintenance therapy. You must not suggest it can be used as a rescue medication'. Representatives were not similarly reminded that they must not promote Seebri Breezhaler for reduction of exacerbations. A subsequent slide appeared to show a page similar to that contained within the sales aid referred to below with the claim, 'Initiate Seebri Breezhaler to reduce your patients' risk of exacerbations'. Overall the Panel considered that the presentation suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated. It was particularly important to make this clear to representatives who might well be asked questions about exacerbation data. A second internal training presentation (ref UK/SBR/15-0215a) was similar in content although it did not contain the statement 'Important Seebri Breezhaler is licensed as a maintenance therapy. You must not suggest it can be used as a rescue medication'. Overall the Panel considered that the presentations suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated; both were ruled in breach of Clause 15.9. The Panel considered that high standards had not been maintained; a breach of Clause 9.1 was ruled.

The Seebri Breezhaler sales aid (UK/SBR/15-0354a) contained a page which was headed 'How can you help delay the time to first moderate to severe COPD exacerbation for your patients' which appeared above a graph comparing the effect of Seebri Breezhaler with that of placebo. The claim at the bottom of the slide read 'Initiate Seebri Breezhaler to reduce your patients' risk of exacerbations'. Finally the Panel noted that although a set of Seebri Breezhaler speaker slides (ref UK/SBR/16-0012) only briefly referred to the positive exacerbation data from Kerwin *et al* (2012) compared with placebo, those results were not put into context by any statement of the licensed indication for the medicine. The Panel considered that the sales aid and the speaker slides both suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated; this was inconsistent with the particulars listed in the Seebri Breezhaler SPC and a breach of Clause 3.2 was ruled. The materials implied that exacerbation reduction was a primary reason to prescribe Seebri Breezhaler. 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 a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its rulings and comments above but considered that the matters were not such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.

During its consideration of the Ultibro Breezhaler material, the Panel noted that much of it referred to the findings of Zhong *et al*, ie a 31% reduction in the rate of moderate or severe exacerbations for Ultibro Breezhaler vs salmeterol/fluticasone (p=0.048). COPD exacerbations over 26 weeks, however, was only an exploratory objective of the study; the primary objective had been to demonstrate the non-inferiority of Ultibro Breezhaler to salmeterol/fluticasone in terms of postdose trough FEV1 at week 26. The exploratory nature of the exacerbation data was stated on some pieces by way of a footnote. In that regard the Panel queried whether exploratory data was robust enough to substantiate the prominent claims made and it also noted the advice contained in the supplementary information to Clause 7.2 that claims should be able to stand alone and in general should not be qualified by footnotes and the like. The Panel was further concerned to note that the data contained in the SPC with regard to COPD exacerbations showed a non-significant benefit for Ultibro Breezhaler vs salmeterol/fluticasone in that it was stated that number of moderate or severe COPD exacerbations/patient years was 0.15 vs 0.18 respectively (p=0.098). In that regard the Panel queried whether claims related to the statistically significant benefit for Ultibro Breezhaler vs salmeterol/fluticasone reported by Zhong *et al* were consistent with the non-significant benefit listed in the Ultibro Breezhaler SPC. The Panel requested that the Alliance be advised of its concerns in this regard.

Complaint received **25 April 2016**

Case completed **16 September 2016**