CASE AUTH/2842/4/16

ANONYMOUS, NON CONTACTABLE v ASTRAZENECA

Promotion of Duaklir Genuair

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 in that regard noted, *inter alia*, AstraZeneca's product Duaklir Genuair (formoterol/aclidinium) for which, according to its EPAR, a specific licence for exacerbation reduction was never applied for.

Duaklir Genuair was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD.

In relation to this case the complainant noted in particular a Duaklir Genuair leavepiece which contained the claim '... Duaklir has been shown to reduce moderate to severe exacerbations...' and a speaker slide set which included data on a competitor to Duaklir Genuair which stated '... Ultibro Breezhaler significantly reduces the rate of severe or moderate COPD exacerbations vs glycopyrronium over 64 weeks...'. The complainant submitted that neither of the above items contained any information warning of the off-label aspects of the promoted products.

The complainant concluded that as there was no specific indication for exacerbation reduction in the registration applications for Duaklir Genuair, the medicine was not licensed for use to reduce exacerbations in COPD patients and so promoting it to reduce COPD exacerbation reduction was off-label.

The complainant stated 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 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 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 AstraZeneca is given below.

The Panel noted that Section 5.1 of the Duaklir Genuair summary of product characteristics (SPC) referred to its positive impact on exacerbations of COPD. 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 as a maintenance bronchodilator therapy to relieve symptoms.

The Panel noted that the leavepiece clearly stated on the front cover 'Twice daily LAMA/LABA combination of aclidinium/formoterol for your COPD patients who remain breathless and require improved symptom control, despite LAMA therapy'. Page 2 introduced Duaklir Genuair and was headed 'The confidence of two trusted molecules for your COPD patients who remain breathless and require improved symptom control, despite LAMA monotherapy'. In boxed text on page 3, the efficacy with regard to symptom control and bronchodilation was briefly referred to followed by 'Furthermore Duaklir has been shown to: reduce moderate or severe exacerbations vs placebo'. The gate folded flap which gave a brief summary of Duaklir Genuair did not refer to the exacerbation data. The Panel considered that the claim for reduced exacerbations vs placebo was presented as a consequence of

using Duaklir Genuair to control COPD symptoms and not as the reason to prescribe the medicine *per se*, as alleged. Given the context in which it appeared, the claim was not misleading with regard to the licensed indication for Duaklir Genuair. High standards had been maintained. No breaches of the Code were ruled.

The Panel noted that the complainant had drawn attention to data on slide 39 of a speaker slide set which stated 'Ultibro Breezhaler significantly reduces the rate of severe or moderate COPD exacerbations vs glycopyrronium over 64 weeks' above a bar chart. In that regard, the Panel noted that Ultibro Breezhaler was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD; it was not licensed to reduce COPD exacerbations. The licensed indication for Ultibro Breezhaler was not stated in the slide set although the introductory slide for that part of the presentation was headed 'Overview of newer bronchodilators treatment of COPD' and listed indacaterol and glycopyrronium separately. Nonetheless, the Panel considered that some might assume that Ultibro Breezhaler could be prescribed *per se* to reduce COPD exacerbations. Although Ultibro Breezhaler appeared to have been promoted for exacerbation reduction, it was not AstraZeneca's medicine and on this narrow point, no breach was ruled. The Panel considered that, on balance, the slide set gave a misleading impression about the licensed indication for Ultibro Breezhaler and in this regard high standards had not been maintained. Breaches of the Code were ruled

In response to the complainant's wider concerns about the promotion of Duaklir Genuair, the Panel noted that the speaker slide set referred to by him/her was a broad discussion on bronchodilators, steroids and the airways over 45 slides. The first slide made it clear that the presentation had been delivered at an AstraZeneca meeting. Although the components of Duaklir Genuair were separately listed on slide 32 as bronchodilators, none of the three specific Duaklir Genuair slides stated the licensed indication for the medicine; slides 33 and 34 detailed lung function and dyspnoea results respectively and then, with apparent equal emphasis, 35 featured a bar chart above which was the claim 'Duaklir was associated with a statistically significant reduction of 29% in the rate of moderate or severe exacerbations'. The Panel considered that in the absence of any statement as to the licensed indication for Duaklir Genuair, the exacerbation data might be viewed by some as the reason to prescribe the medicine as alleged rather than a benefit of using the medicine as maintenance therapy. The slide set was inconsistent with the particulars listed in the Duaklir Genuair SPC and was misleading with regard to the licensed indication for Duaklir Genuair and breaches of the Code were ruled including that high standards had not been maintained.

In the Panel's view the briefing materials did not show that representatives had been encouraged to promote Duaklir Genuair for reduction in COPD exacerbation as alleged. Any reference to such data was clearly set within the context of the licensed indication. No breach of the Code was ruled.

Neither an A4 card headed 'LABA/LAMA combination therapy in COPD' or a booklet about understanding patient-reported outcomes in COPD promoted Duaklir Genuair for reduction in COPD exacerbations. The pieces were not misleading as to the licensed indication for Duaklir Genuair. No breaches of the Code were ruled including that high standards had been maintained.

A third promotional piece entitled 'Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD; pooled analysis of symptoms and exacerbations from two six month, multicentre, randomised studies (ACLIFORM and AUGMENT)' did not clearly set out the licensed indication for Duaklir Genuair. Although symptom scores were discussed before exacerbations, the two were given equal emphasis. In that regard the Panel considered that some readers might assume that Duaklir Genuair could be prescribed, *per se*, to reduce COPD exacerbations for which the medicine was not licensed. This was inconsistent with the particulars listed in its SPC and was misleading about the licensed indication. Breaches of the Code were ruled including that high standards had not been maintained.

AstraZeneca had provided copies of 28 slides sets in addition to the one cited by the complainant. None of the slide sets clearly and unequivocally set out the licensed indication for Duaklir Genuair. Although exacerbation data was often referred to after data relating to symptom control, it appeared to be given the same emphasis. None of the slide sets stated that Duaklir Genuair was not licensed for reduction in exacerbations. One slide set listed as reasons to prescribe Duaklir Genuair, improved symptoms, reduced risk of rescue inhaler and reduced risk of exacerbation without making any distinction between symptom control and reduced exacerbations; a second slide set similarly listed 'Reduce exacerbations' in a list of the outcomes to be expected with therapy. A third slide set concluded that the place of LABA/LAMA in the treatment pathway was to address symptoms and exacerbations. The Panel considered that in the absence of any statement as to the licensed indication for Duaklir Genuair, the exacerbation data might be viewed by some as the reason to prescribe the medicine which was not in accordance with its SPC. Given the context in which the exacerbation data appeared, and the equal emphasis it appeared to have been given compared with symptom control, the slide sets were misleading with regard to the licensed indication for Duaklir Genuair. Breaches of the Code were ruled including that high standards had not been maintained.

The Panel noted its comments and rulings above and in particular it noted the extent to which AstraZeneca had facilitated independent speakers to present data on Duaklir Genuair without ensuring that its licensed indication was properly and unambiguously communicated to the audience, and further ensuring that exacerbation data was only referred to within the context of using the medicine to relieve COPD symptoms. The Panel was very concerned to note that speaker slides were only examined and not

formally certified given their promotional content and the inclusion of Duaklir Genuair slides which appeared to have been generated by AstraZeneca. This was of particular concern given their use at field force speaker meetings and the influence that local independent speakers would have on their colleagues. The first slide of each presentation clearly stated 'This is an AstraZeneca meeting'. Given the company's involvement and the context in which they were delivered, the presentations were clearly promotional and AstraZeneca was responsible for their content despite the disclaimer which appeared on every presentation that 'The views expressed by the speaker are not necessarily those of AstraZeneca'. In the Panel's view, facilitating the use by independent speakers on the company's behalf, of uncertified promotional presentations brought discredit upon, and reduced confidence in, the pharmaceutical industry. A 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 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 ruling of LABA-LAMA combination inhaler indications and in that regard drew attention, *inter alia*, to AstraZeneca's product Duaklir Genuair (formoterol/aclidinium) for which, according to its EPAR, a specific licence for exacerbation reduction was never applied for.

Duaklir Genuair was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD.

COMPLAINT

In relation to this case the complainant drew particular attention to a Duaklir Genuair leavepiece (ref GL/ABF/1214/0063) which contained the claim '... Duaklir has been shown to reduce moderate to severe exacerbations...' and a speaker slide set (ref JRD 02 April 2015, prepared March 2015) which included data on a competitor to Duaklir Genuair which stated '... Ultibro Breezhaler significantly reduces the rate of severe or moderate COPD exacerbations vs glycopyrronium over 64 weeks...'. The complainant submitted that neither of the above items contained any information warning of the off-label aspects of the promoted products.

The complainant submitted that as there was no specific indication for exacerbation reduction in the registration applications for Duaklir Genuair, it could be concluded that the medicine was not licensed for use to reduce exacerbations in COPD patients. Therefore promotion of Duaklir Genuair in relation to COPD exacerbation reduction was off-label.

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 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 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.

In writing to AstraZeneca, 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

AstraZeneca noted that Duaklir Genuair was indicated to relieve symptoms in COPD patients. However, additional endpoint data derived from the pooled phase 3 clinical trials describing reductions in exacerbations were presented in Section 5.1 of

the summary of product characteristics (SPC) which stated:

> 'COPD exacerbation reductions
>
> Pooled efficacy analysis of the two 6-month Phase III studies demonstrated a statistically significant reduction of 29% in the rate of moderate or severe exacerbations (requiring treatment with antibiotics or corticosteroids or resulting in hospitalisations) with Duaklir Genuair compared to placebo (rates per patient per year: 0.29 vs. 0.42, respectively; p=0.036).
>
> In addition, Duaklir Genuair statistically significantly delayed the time to first moderate or severe exacerbation compared to placebo (hazard ratio=0.70; p=0.027).'

AstraZeneca thus considered that the presentation of this exacerbation data was in accordance with the terms of the marketing authorization for Duaklir, not inconsistent with the particulars listed in the SPC and was not in breach of Clause 3.2. Further, the leavepiece at issue was derived directly from a generic (general) leavepiece that was pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA).

In a letter of 12 December 2014, the MHRA stated that it did not object to the leavepiece and accepted its use subject to unrelated minor considerations. One of the principal purposes of the MHRA pre-vetting was to ensure that promotional material complied with the marketing authorization for the product and as such AstraZeneca considered this further supported its position of no breach of Clause 3.2.

AstraZeneca submitted that the overall marketing strategy for Duaklir Genuair since its launch in 2015 had sought to ensure that the presentation of the outcomes from the two phase 3 clinical studies (ACLIFORM and AUGMENT) was balanced and fair with emphasis given to the primary endpoint of lung function (forced expiratory volume in 1 second (FEV1)) and the endpoints relating to the relief of symptoms. Study findings about exacerbations had been reported secondarily in line with the data in the SPC. This was demonstrated in the two items at issue along with the supporting briefing materials.

The leavepiece was part of the launch campaign for Duaklir Genuair in 2015 and was made available to the representatives at the launch conference in January and thereafter; it was widely used with health professionals but had not been used since June 2015 when the colour of the Duaklir Genuair device was changed from white and blue to white and orange.

AstraZeneca submitted that the exacerbation data from the pooled phase 3 clinical trials in the leavepiece were supported by the references cited and were balanced within the context of the item and sequence of statements, were accurate and were not misleading. AstraZeneca thus denied a breach of Clause 7.2.

The leavepiece was a small fold out design which consisted of a front page, a back page with prescribing information and three inner pages which showed information about the product. The central inner page bore the exacerbation data and began with a statement 'Help relieve the symptoms of COPD for your patients who need improved symptom control'. The subsequent statements on this page referred to the key primary and secondary endpoints from the clinical studies ie bronchodilation, breathlessness and overall symptom control, consistent with the licensed indication for the product.

The statement about exacerbations on the central page was shown as a bullet point placed third in a list within a text box. It was referenced to a poster which described the exacerbation findings from the pooled analysis of the two phase 3 clinical trials of Duaklir Genuair and read:

> 'Furthermore Duaklir has been shown to: reduce moderate to severe exacerbations vs. placebo.'

AstraZeneca submitted that the depiction of the exacerbation data from the phase 3 Duaklir Genuair clinical trials within the leavepiece was given fair prominence, was factual, accurate, balanced and not misleading and thus, not a breach of Clause 7.2.

With regard to the speaker slide set referred to by the complainant, AstraZeneca noted that it was written by an internationally renowned UK professor of respiratory medicine and approved for use at a number of representative run speaker meetings for health professionals. These slides were examined and approved in April 2015 before use by a medical nominated signatory in accordance with company policy. As the slides were examined, a certificate was not produced.

The presentation was to support a talk entitled 'Bronchodilation, Steroids and the Airway – What next?' The first 32 of the 45 slide deck discussed phenotype-based management of COPD and showed data from a number of published clinical trials. Slides 33 to 35 showed clinical data from the Duaklir Genuair phase 3 clinical studies in the following sequence:

- Slide 33 showed the findings for one of the co-primary endpoints, ie lung function at one hour post-morning dose compared with Duaklir Genuair's components and placebo. Further detailed speaker notes were available within the presentation.
- Slide 34 presented breathlessness findings as measured by the transitional dyspnoea index (TDI) and showed data from the pooled analysis and the two studies individually.
- Slide 35 depicted the exacerbations outcomes in the studies as a bar graph; the y axis showed the actual rates of exacerbations per patient per year and the x axis showed the two sets of data, 'all exacerbations' and 'moderate to severe exacerbations' for the placebo, aclidinium, formoterol and combination product. Risk ratio figures were shown between the combination

product and placebo and the p values for these differences was in notes below the graph which also defined moderate or severe exacerbation.

More detailed speaker notes for this exacerbation data graph stated:

> 'Analysis of the rate of exacerbations was assessed as a secondary outcome, based on the pooled data from ACLIFORM and AUGMENT (3,394 patients), as the studies were not powered to look at exacerbations, and as the study populations were not enriched for exacerbations, the rate of exacerbation was relatively low. As shown here, treatment with Duaklir was associated with a statistically significant reduction of 29% in the rate of moderate or severe exacerbations (based on healthcare resource utilisation [HCRU] criteria) compared with placebo ($p<0.05$) and a risk reduction of 24% for exacerbations of any severity, although this did not reach significance.'

The exacerbation data from the two pivotal phase 3 Duaklir Genuair clinical trials depicted in the slide presentation were supported by the references cited, were balanced within the context of the item, were accurate and were not misleading.

Following the slides showing Duaklir Genuair data were 4 slides from the Ultibro Breezhaler clinical study programme. Each slide accurately detailed the results of the study's primary endpoint with the sources of this information cited on each slide.

AstraZeneca stated that the overall presentation of data for LAMA/LABAs in the slides was not in breach of Clause 7.2.

With regard to supporting items for the representatives, AstraZeneca provided copies of the esales aid briefing guide (ref GL/ABF/0115/0184) and a table of marketing and educational materials available to representatives (ref GL/ABF/0115/0208).

The representatives underwent a comprehensive remote and face-to-face training programme in order to be fully trained and validated on the technical aspects of Duaklir Genuair. Furthermore, they received specific instructions as to how to present the exacerbation data from the two phase 3 pivotal clinical studies within the context of the overall campaign. AstraZeneca included two examples of certified briefing material, to illustrate how the representatives were specifically briefed to discuss exacerbation data for Duaklir Genuair.

The esales aid briefing guide contained the briefing for the overall promotion of Eklira (aclidinium) and Duaklir Genuair. The flow of the promotional messages for Duaklir Genuair was balanced and prioritised the discussion of its effects on symptom control and bronchodilation. Slide 46 of the briefing guide, listed the findings from the pivotal phase 3 Duaklir Genuair clinical studies relating to exacerbations as one of six key messages for the product and used the same language and references as the leavepiece at issue. The next 4 slides described the electronic sales aid screens to be used as the core flow for Duaklir Genuair and cited breathlessness, symptom control and lung function clinical study findings.

There were instructions that accompanied a screen available in the electronic sales aid which bore a bar graph depicting the pooled data from the phase 3 Duaklir Genuair clinical studies for moderate and severe exacerbations. Representatives were instructed that this was not a core page but could be used 'reactively in response to questions around exacerbations'.

Briefing of the leavepiece was within a document 'Marketing and Educational Materials Available to Representatives', which itemised all the materials available at launch. It stated that the leavepiece should be used as a post-call reminder or at meetings and set out the key messages to be taken from the item ie that Duaklir Genuair improved breathlessness, overall symptom control and bronchodilation vs aclidinium and formoterol given individually. Exacerbations outcomes were not cited as a key message to be taken from this item.

AstraZeneca noted that further details of the training programme for Duaklir Genuair representatives could be made available upon request.

In summary AstraZeneca submitted that representatives were suitably instructed on the technical aspects of Duaklir Genuair and how it should be promoted and it denied a breach of Clause 15.9 of the Code.

In response to a request for further information, AstraZeneca reiterated that it was confident that its depiction of the Duaklir Genuair exacerbation data was consistent with the particulars listed in the SPC and did not breach Clause 3.2. This was supported by the inclusion of the exacerbation findings in Section 5.1 of the SPC and the acceptance of similar representation of the data in the launch materials pre-vetted by the MHRA. Furthermore, the Duaklir Genuair exacerbation data from the phase 3 pivotal trials was given fair prominence, was factual, accurate, and balanced and hence not in breach of Clause 7.2.

AstraZeneca provided copies of all its current marketing items and associated briefing documents that referred to the Duaklir Genuair exacerbation data. The company submitted that in all of these documents, the exacerbation data from the pooled clinical studies was depicted in accordance with the terms of the Duaklir Genuair marketing authorization and consistent with the particulars listed in the SPC. The data was presented in a balanced and fair manner consistent with the depiction and emphasis given to this data from the original 2015 launch campaign, the leavepiece from which was cited by the complainant and discussed in detail above.

With regard to external speaker authored slide decks, AstraZeneca stated that its policy was to medically review such before use. These decks were then available for use for six months provided no alterations

were made. All current speaker decks to support Duaklir Genuair had been reviewed and of these, 28 cited the Duaklir Genuair exacerbation outcomes data and had thus been considered relevant to this case and a summary of each was provided. In all 28 decks the exacerbation data was depicted in accordance with the terms of the Duaklir Genuair marketing authorization and consistent with the particulars listed in the SPC and did not breach Clause 3.2.

In 25 of the 28 decks, including the presentation cited by the complainant, the Duaklir Genuair exacerbation data was presented after presentation of data on symptom control and/or lung function, and reflected a fair, balanced and accurate depiction of the evidence. Three decks presented the Duaklir Genuair exacerbation data in a different sequence, however, these decks were overall balanced and thus did not breach Clause 7.2. Two of the decks were variations of a deck written by the same author as detailed below:

- [named individual] March 2016

In this deck Duaklir Genuair exacerbation data was shown in slide 20 of 35 within the context of a presentation on the impact of COPD exacerbation of a number of licenced inhaled medicines. There then followed in slides 27-32 data on the outcomes from the Duaklir Genuair phase 3 studies on lung function, breathlessness, symptom control and quality of life.

- [named individual] February 2016 and April 2016

This deck of 66 slides presented various important clinical issues in COPD, including smoking cessation and pulmonary rehabilitation. Slide 40 introduced lung function and breathlessness/symptom control data from clinical studies of aclidinium. There then followed data from Duaklir Genuair clinical studies in slides 47-49. The Duaklir Genuair exacerbation data was presented from the pooled data and there followed data on symptom control and quality of life.

AstraZeneca denied breaches of Clauses 3.2 and 7.2 with regard to its current marketing materials and current externally authored slide decks for speaker meetings.

PANEL RULING

The Panel noted that Duaklir Genuair was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. Section 5.1 of the SPC referred to its positive impact on exacerbations of COPD. 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 as a maintenance bronchodilator therapy to relieve symptoms.

The Panel noted that AstraZeneca 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 are made under the 2016 Code.

The Panel noted that the leavepiece at issue (ref GL/ABF/1214/0063) clearly stated on the front cover 'Twice daily LAMA/LABA combination of aclidinium/formoterol for your COPD patients who remain breathless and require improved symptom control, despite LAMA therapy'. Page 2 introduced Duaklir Genuair and was headed 'The confidence of two trusted molecules for your COPD patients who remain breathless and require improved symptom control, despite LAMA monotherapy'. In boxed text on page 3, the efficacy with regard to symptom control and bronchodilation was briefly referred to followed by 'Furthermore Duaklir has been shown to: reduce moderate or severe exacerbations vs placebo'. The gate folded flap which gave a brief summary of Duaklir Genuair did not refer to the exacerbation data. The Panel considered that the claim for reduced exacerbations vs placebo was presented as a consequence of using Duaklir Genuair to control COPD symptoms and not as the reason to prescribe the medicine *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 Duaklir Genuair. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel noted that the complainant had drawn attention to data on slide 39 in a speaker slide set (ref JRD 02 April 2015) which stated 'Ultibro Breezhaler significantly reduces the rate of severe or moderate COPD exacerbations vs glycopyrronium over 64 weeks' above a bar chart. In that regard, the Panel noted that Ultibro Breezhaler was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD; it was not licensed to reduce COPD exacerbations. The licensed indication for Ultibro Breezhaler was not stated in the slide set although the introductory slide (slide 32) for that part of the presentation was headed 'Overview of newer bronchodilators treatment of COPD' and listed indacaterol and glycopyrronium separately. Nonetheless, the Panel considered that some might assume that Ultibro Breezhaler could be prescribed *per se* to reduce COPD exacerbations. Clause 1.2 of the Code defined promotion as any activity undertaken by a company which promoted the administration, consumption, prescription, purchase recommendation, sale supply or use of *its* medicines (emphasis added). Clause 3.2 prohibited the promotion of a medicine outwith the terms of its marketing authorization. Although Ultibro Breezhaler appeared to have been promoted for exacerbation reduction, it was not AstraZeneca's medicine and on this narrow point, no breach of Clause 3.2 was ruled. Clause 7 of the Code, however, referred to information, claims and comparisons

and in that regard applied to what a company stated about its own medicine and what it stated about competitors. The Panel considered that, on balance, the slide set gave a misleading impression about the licensed indication for Ultibro Breezhaler and it ruled a breach of Clause 7.2. High standards had not been maintained. A breach of Clause 9.1 was ruled.

In response to the complainant's wider concerns about the promotion of Duaklir Genuair, the Panel noted that the speaker slide set referred to by the complainant (ref JRD 02 April 2015), was a broad discussion on bronchodilators, steroids and the airways over 45 slides. The first slide made it clear that the presentation had been delivered at an AstraZeneca meeting. Although the components of Duaklir Genuair were separately listed on slide 32 as bronchodilators, none of the three specific Duaklir Genuair slides stated the licensed indication for the medicine; slides 33 and 34 detailed lung function and dyspnoea results respectively and then, with apparent equal emphasis, 35 featured a bar chart above which was the claim 'Duaklir was associated with a statistically significant reduction of 29% in the rate of moderate or severe exacerbations'. The Panel considered that in the absence of any statement as to the licensed indication for Duaklir Genuair, the exacerbation data might be viewed by some as the reason to prescribe the medicine as alleged rather than a benefit of using the medicine as maintenance therapy. The slide set was inconsistent with the particulars listed in the Duaklir Genuair SPC and in that regard a breach of Clause 3.2 was ruled. Given the context in which it appeared, the claim about exacerbation reduction was misleading with regard to the licensed indication for Duaklir Genuair and implied that exacerbation reduction was the primary reason to prescribe. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

AstraZeneca had provided a copy of the esales aid briefing guide (ref GL/ABF/0115/0184). The Panel noted that the emphasis from the outset (slide 41) was on the use of Duaklir for COPD patients who needed improved symptom control despite LAMA monotherapy; reference to exacerbation reduction was secondary to improvements in breathlessness, overall symptom control and bronchodilation. There was a pop-up screen detailing reductions in moderate or severe exacerbations but this was only to be used reactively in response to questions about exacerbations. The Table of Marketing and Educational Materials Available to Representatives listed all of the materials available each with a key visual, description and key messages. All of the key messages for Duaklir related to its use for additional symptom control, none referred to exacerbation reduction. In the Panel's view the briefing materials did not show that representatives had been encouraged to promote Duaklir Genuair for reduction in COPD exacerbation as alleged. Any reference to such data was clearly set within the context of the licensed indication. No breach of Clause 15.9 was ruled.

AstraZeneca provided copies of two further promotional pieces; an A4 card headed 'LABA/LAMA combination therapy in COPD' (ref 889,022.011, October 2015) and a booklet about understanding patient-reported outcomes in COPD (ref 951,333.011, February 2016). The booklet bore the product name and logo prominently in the top left of the front cover. Neither item discussed exacerbation data with specific reference to Duaklir. In that regard the Panel did not consider that either piece promoted Duaklir Genuair for reduction in COPD exacerbations. No breach of Clause 3.2 was ruled. The pieces were not misleading as to the licensed indication for Duaklir Genuair. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

A third promotional piece (ref 929,977.011, January 2016) provided by AstraZeneca was entitled 'Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD; pooled analysis of symptoms and exacerbations from two six month, multicentre, randomised studies (ACLIFORM and AUGMENT)'. The Panel noted that there was no clear statement in the body of the piece which clearly set out the licensed indication for Duaklir Genuair. Although symptom scores were discussed before exacerbations, the two were given equal emphasis. In that regard the Panel considered that some readers might assume that Duaklir Genuair could be prescribed, *per se*, to reduce COPD exacerbations for which the medicine was not licensed. This was inconsistent with the particulars listed in its SPC. A breach of Clause 3.2 was ruled. The piece was misleading about the licensed indication for Duaklir Genuair. A breach of Clause 7.2 was ruled. In the Panel's view, high standards had not been maintained. A breach of Clause 9.1 was ruled.

AstraZeneca had provided copies of 28 slides sets in addition to the one cited by the complainant. None of the slide sets clearly and unequivocally set out the licensed indication for Duaklir Genuair. Although exacerbation data was often referred to after data relating to symptom control, it appeared to be given the same emphasis. None of the slide sets stated that Duaklir Genuair was not licensed for reduction in exacerbations. One slide set (ref JRD 01 April 2016) listed as reasons to prescribe Duaklir Genuair, improved symptoms, reduced risk of rescue inhaler and reduced risk of exacerbation without making any distinction between symptom control and reduced exacerbations; a second slide set (ref December 2015 SWD) similarly listed 'Reduce exacerbations' in a list of the outcomes to be expected with therapy. A third slide set (ref February 2016 SWD) concluded by stating that the place of LABA/LAMA in the treatment pathway was to address symptoms and exacerbations. The Panel considered that in the absence of any statement as to the licensed indication for Duaklir Genuair, the exacerbation data might be viewed by some as the reason to prescribe the medicine which was not in accordance with its marketing authorization as alleged. In that regard a breach of Clause 3.2 was ruled. Given the context in which the exacerbation data appeared, and the equal emphasis it appeared to have been given compared with symptom control, the slide sets were misleading with regard to the licensed indication for Duaklir Genuair. 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 its comments and rulings above and in particular it noted the extent to which AstraZeneca had facilitated independent speakers to present data on Duaklir Genuair without ensuring that its licensed indication was properly and unambiguously communicated to the audience, and further ensuring that exacerbation data was only referred to within the context of using the medicine to relieve COPD symptoms. The Panel was very concerned to note that speaker slides were only examined and not formally certified given their promotional content and the inclusion of Duaklir Genuair slides which appeared to have been generated by AstraZeneca. This was of particular concern given their use at speaker meetings organised by the field force such as slide set 951,913.001 which was clearly promotional. In the Panel's view, this was of particular concern given the influence that local independent speakers would have on their colleagues. The first slide of each presentation clearly stated 'This is an AstraZeneca meeting'. Given the company's involvement and the context in which they were delivered, the presentations were clearly promotional and AstraZeneca was responsible for their content despite the disclaimer which appeared on every presentation that 'The views expressed by the speaker are not necessarily those of AstraZeneca'. In the Panel's view, facilitating the use by independent speakers on the company's behalf, of uncertified promotional presentations brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **25 April 2016**

Case completed **16 September 2016**