CASE AUTH/2588/3/13

THE DRUG AND THERAPEUTICS BULLETIN v NOVARTIS

Promotion of Seebri Breezhaler

The Drug and Therapeutics Bulletin complained about a booklet entitled 'Evidence Review of Seebri Breezhaler (glycopyrronium bromide)' issued for use in formulary packs by Novartis. Seebri Breezhaler was indicated for use in adults with chronic obstructive pulmonary disease (COPD).

The complainant alleged that page 6 of the Evidence Review contained an unsubstantiated argument for the treatment of COPD exacerbations. Under a sub-heading, 'The importance of reducing exacerbations', the second bullet point stated 'Mortality following hospital admission is higher in patients suffering a COPD exacerbation than those with a myocardial infarction at 12 months [Halpin 2008]. The 180 day mortality rate following a COPD exacerbation is 33% [Anzueto 2010] and therefore reductions in exacerbations can reduce mortality rates'.

The 180 day mortality rate following a COPD exacerbation was not 33%. Anzueto was a review article that highlighted the high mortality rate in patients admitted to hospital with an acute exacerbation of COPD. The paper cited Connors *et al* (1996) which compared outcomes in a particularly ill group of patients with acute hypercapnic respiratory failure. The Evidence Review did not clarify the group of patients to which this data applied. The complainant alleged that the statement was unhelpful and misleading.

A literature search showed that the conclusion 'and therefore reductions in exacerbations can reduce mortality rates' had not been proven. Mortality rates were higher in frequent exacerbators than infrequent exacerbators but the complainant was unaware of any study that had shown that reducing exacerbations with treatments lowered mortality. Data suggested that tiotropium might be more effective than long-acting beta agonists (Vogelmeier *et al* 2011)) but even a four year study in which mortality was a secondary endpoint failed to demonstrate a benefit from the use of tiotropium (Tashkin *et al* 2008).

The impact of glycopyrronium on exacerbations was a secondary endpoint in all the trials cited. Although the Evidence Review clarified primary and secondary endpoints, it presented data for the secondary endpoint first. Given the juxtaposition of the statements on mortality and exacerbations with the secondary endpoint data on exacerbations, readers might apply more weight to the information than was supported by evidence.

The detailed response from Novartis is given below.

The Panel noted that Anzueto reviewed, *inter alia*, the impact of exacerbations on mortality and noted that Connors *et al* reported that in patients admitted to hospital with acute hypercapnic respiratory failure, the 180 day mortality rate was 33%. The complainant stated that this was a particularly ill group of patients and that the 180 day mortality rate was not 33%. The complainant had not stated whether he considered the 180 day mortality rate to be more or less than 33%. The Panel noted that Seneff *et al* reported that in a group of patients aged 65 years or older admitted to intensive care primarily with an acute exacerbation of COPD, 180 day mortality was 47%. The Panel noted the difference in 180 day mortality rates between the two groups and also that there was no way of comparing the COPD severity of the two groups. Given the difference in the 180 day mortality rate reported in the literature, the Panel considered that the unqualified, unconditional claim 'The 180 day mortality rate following a COPD exacerbation is 33%' was misleading. It implied that the 180 day mortality in any patient following a COPD exacerbation had been categorically proven to be 33% which was not so. Breaches of the Code were ruled.

The Panel noted that the claim, 'and therefore reductions in exacerbations can reduce mortality rates', was not referenced. The Panel did not accept Novartis' submission that the claim was not linked to any specific treatment. Given the data on the facing page about Seebri Breezhaler and exacerbations there was an inference that Seebri Breezhaler would have a positive impact on mortality. The Panel further noted Novartis's submission that no single study had successfully demonstrated that a specific COPD treatment had decreased overall mortality. Halpin reviewed COPD treatment and noted that although the ISOLDE study showed that inhaled fluticasone significantly reduced the rate of exacerbations, a post hoc analysis only showed a non-significant trend towards improved survival (Briggs *et al* 2006). However, in the TORCH study, although fluticasone reduced the rate of exacerbation, it did not show a reduction in all-cause mortality at 3 years vs placebo (Calverley *et al* 2007). Halpin also reported that tiotropium had been shown to reduce exacerbation frequency and that a post hoc analysis suggested that it might reduce the rate of decline of FEV1; if this was a real effect then it might have an effect on mortality. Halpin further reported the benefits to COPD patients in preventing exacerbations of adding inhaled corticosteroids to long-acting B2-agonists but the studies cited did not link this benefit to a decrease in mortality. Conversely, other studies which examined the impact of adding inhaled corticosteroids to bronchodilator therapy did not link the reduced risk of death with a reduced rate of exacerbation. Halpin acknowledged that the studies reviewed, with the exception of the

TORCH study, were not designed to assess mortality rates – most were underpowered as death was an uncommon event. The Panel noted that the complainant had referred to Tashkin *et al* and Vogelmeier *et al*, neither of which had been cited by Halpin. The complainant noted that these studies showed that although tiotropium was possibly more effective than long-acting B2-agonists, in a study that compared time to first exacerbation of COPD, a four year study in which mortality was a secondary endpoint failed to demonstrate a benefit from the use of tiotropium.

Overall, the Panel considered that although the strong claim that 'reductions in exacerbations can reduce mortality rates' appeared to be self-evident, it did not reflect the balance of the data. The claim implied that reducing COPD exacerbations with treatment had been unequivocally shown to reduce mortality rates which was not so. The Panel considered that the claim was misleading as alleged and could not be substantiated. Breaches of the Code were ruled.

The Panel noted that the page facing that considered above was headed 'Glycopyrronium and exacerbations' and featured a table which detailed the secondary outcomes from the GLOW-1 study (glycopyrronium vs placebo) and the GLOW-2 study (glycopyrronium vs tiotropium). In both studies the primary efficacy endpoint was trough FEV1 at 12 weeks. Above the table was an explanation that a secondary objective of the two studies was to explore the first COPD exacerbation with glycopyrronium vs placebo over 26 weeks (GLOW-1) and 52 weeks (GLOW-2). Exploratory endpoints for GLOW-2 also included measuring the effect of glycopyrronium vs tiotropium in time to first exacerbation. The table, however, had two columns headed 'Endpoint' and 'Result' and so the secondary nature of the endpoints detailed within was not immediately obvious. The Panel considered that the explanation of the endpoints above the table was not prominent and thus was insufficient in this regard. The Panel considered that the presentation of the data was not sufficiently complete to allow the reader to appreciate its statistical significance and the table was misleading in that regard. A breach of the Code was ruled.

Given its rulings above, the Panel ruled a further breach as high standards had not been maintained.

The Drug and Therapeutics Bulletin complained about a 16 page 'Evidence Review of Seebri Breezhaler (glycopyrronium bromide)' (ref SBH12-CO17) issued for use in formulary packs by Novartis Pharmaceuticals UK Ltd. Seebri Breezhaler was indicated as maintenance bronchodilator treatment to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD).

COMPLAINT

The complainant alleged that the Evidence Review made an unsubstantiated argument for the treatment of exacerbations. Under a sub-heading on page 6, 'The importance of reducing exacerbations', the second bullet point stated 'Mortality following hospital admission is higher in patients suffering a COPD exacerbation than those with a myocardial infarction at 12 months [Halpin 2008]. The 180 day mortality rate following a COPD exacerbation is 33% [Anzueto 2010] and therefore reductions in exacerbations can reduce mortality rates'.

The complainant stated that the first part of the final sentence was incorrect. The 180 day mortality rate following a COPD exacerbation was not 33%. Anzueto was a review article that highlighted the high mortality rate in a group of patients admitted to hospital with an acute exacerbation of COPD. The paper cited Connors *et al* (1996) which compared outcomes in patients admitted to hospital with an exacerbation of COPD and a Pa_{CO_2} (arterial carbon dioxide tension) of 50mmHg or more (in other words, a particularly ill group of patients with acute hypercapnic respiratory failure). The Evidence Review did not clarify the group of patients to which this data applied. The complainant alleged that the statement was unhelpful and misleading.

More importantly however, was the conclusion of the final sentence 'and therefore reductions in exacerbations can reduce mortality rates'. Whilst the complainant had every desire that this was the case, a thorough literature search showed that this had not been proven. Mortality rates were higher in frequent exacerbators than infrequent exacerbators but the complainant was unaware of any study that had shown that reducing exacerbations with treatments lowered mortality. There was data that suggested that tiotropium might be more effective than long-acting beta agonists (in a study that compared time to first exacerbation of COPD as the primary endpoint, (Vogelmeier *et al* 2011)) but even a four year study in which mortality was a secondary endpoint failed to demonstrate a benefit from the use of tiotropium (Tashkin *et al* 2008).

The complainant further stated that the impact of glycopyrronium on exacerbations was a secondary endpoint in all the trials cited. Although the Evidence Review clarified primary and secondary endpoints, it presented data for a secondary endpoint first. The juxtaposition of the statements on mortality and exacerbations with the secondary endpoint data on exacerbations might lead readers to apply more weight to the information than was supported by evidence.

When writing to Novartis the Authority requested that it consider the requirements of Clauses 7.2, 7.4 and 9.1.

RESPONSE

Novartis submitted that the SUPPORT study (Connors *et al*) referenced by Halpin and Anzueto was selected to illustrate the point about a high (33%) 180 day mortality rate relating to exacerbations. The SUPPORT trial was a high quality, prospective trial with a large trial population, with consequently a large number of exacerbation

events. The patients in the SUPPORT study all had exacerbations leading to hospitalisation and experienced hypercapnoea. Whilst it had been demonstrated that post-exacerbation mortality in patients with hypercapnoea was higher than those with normal ventilation, the impact of severe exacerbation frequency had been demonstrated to have a significantly higher impact on mortality risk compared with the increased risk of mortality relating to hypercapnoea (Soler-Cataluña *et al* 2005).

Another study, the APACHE-III trial (Seneff *et al* 1995) demonstrated that 180 day mortality following an exacerbation which required hospitalisation for patients over 65 years of age was 47%. Therefore the figure quoted in the Evidence Review document at issue indicated that a figure of 33% from the SUPPORT study was not exaggerated and reflective of the incidence of 180 day mortality following hospitalisation.

Seebri Breezhaler was licensed for maintenance bronchodilator treatment of COPD and so the patients in this study would have been within licence. Novartis was therefore confident that it was not necessary to further clarify the group of patients to which these data applied as they were all defined as having COPD. The focus of page 6 charted the potential for progression of COPD as a chronic illness with exacerbations and the improvements for disease management by early intervention. Novartis submitted therefore that this claim represented the available evidence for outcomes of COPD exacerbations and thus it denied a breach of Clauses 7.2 or 7.4.

With regard to the claim 'reductions in exacerbations can reduce mortality rates', Novartis submitted that there was no specific mention of reducing exacerbation rate by any specific treatment at this point in the material at issue. This section was intended to give a brief summary of exacerbations and the impact of exacerbation upon COPD patients and did not make any claims regarding the impact of specific treatments.

It had been well documented that exacerbations had a strong impact on both morbidity and mortality of COPD patients. Halpin specifically stated 'Severe exacerbations of COPD have been shown to be associated with a worse prognosis, and mortality increases with the frequency of exacerbations. Exacerbations of COPD severe enough to require hospitalisation have a significantly greater effect on mortality than those which can be managed in the community'. This was specifically demonstrated by Soler-Cataluña *et al* (2005) which demonstrated that patients with a single unplanned hospital admission had a significantly poorer survival rate than those with no acute exacerbations or COPD or who were not admitted to hospital, and risk of mortality increased with exacerbation frequency to the point where the patients with the greatest mortality risk (of all patient factors considered) were those with three or more acute exacerbations of COPD. Soler-Cataluña *et al* (2009) demonstrated that patients with one or two severe exacerbations had an adjusted mortality risk increased by 2.24-fold, whilst those patients with three or more had an adjusted mortality risk increased by 2.80-fold, thereby demonstrating a clear link between increased exacerbation rate and increased mortality risk. Additionally, Hansel and Barnes (2009) described the impact of exacerbations on disease progression that demonstrated how exacerbations led to accelerated loss of lung function and increasing progression of COPD, which would ultimately lead to increased risk of mortality as the disease progressed. This accelerated decline was specifically illustrated in the paper.

Novartis submitted that other authors had discussed a correlation between reduced exacerbation rates and reductions in mortality: Garcia-Aymerich *et al* (2006) reported that COPD patients with higher than 'very low' physical activity demonstrated a reduction in both hospital admissions and overall mortality risk. Based on this data pulmonary rehabilitation, a frequently used treatment for COPD patients which promoted exercise and prevented further deconditioning, was likely to have a positive effect on exacerbations and therefore mortality. Similarly, a meta-analysis of 22 randomised trials of patients with COPD, Salpeter *et al* (2006) demonstrated that anti-muscarinic compounds demonstrated a reduction in exacerbations of COPD of 33% and a corresponding reduction in mortality of 73% which, despite the potential weaknesses of a small number of the studies in the meta-analysis, clearly highlighted a link between reducing exacerbations and improved mortality.

Novartis stated that scientific and clinical evidence clearly demonstrated that increased numbers of COPD exacerbations increased the overall mortality risk, and there was a clear increase in mortality risk that correlated with the frequency of exacerbations in a year. It thus not only stood to reason but, as stated above, there was data that suggested reducing exacerbation rates could reduce the risk of mortality. Novartis acknowledged, as noted by the complainant, that no single study had successfully demonstrated that a specific treatment for COPD had decreased overall mortality, however, the claim in question did not refer to a specific treatment, and was more a reflection of current medical opinion that reducing exacerbations (using a combination of pharmacological and non-pharmacological treatments and lifestyle changes) led to a significant improvement in the risk of both morbidity and mortality in COPD patients.

Novartis submitted that as the claim reflected current medical opinion in this therapy area and was based on the well established link between exacerbation frequency and mortality rather than the effect on exacerbation frequency of specific treatments, it did not breach Clauses 7.2 or 7.4.

Finally, in response to the complainant's final point of undue weight being given to the exacerbation data from the glycopyrronium studies, it had been clearly stated what the primary and secondary endpoints of the study were, and the reader was not

led into any perception that the exacerbation data was the primary focus of the study. Novartis thus denied a breach of the Code in this regard.

Given the above, Novartis did not consider that it had failed to maintain high standards and it thus denied a breach of Clause 9.1.

PANEL RULING

The Panel noted that the claims at issue appeared as part of the final bullet point on page 6 of the Evidence Review. The claim 'The 180 day mortality rate following a COPD exacerbation is 33%' was referenced to Anzueto, a review of the impact of exacerbations on COPD. The author reviewed, *inter alia*, the impact of exacerbations on mortality and noted that Connors *et al* reported that in patients admitted to hospital with acute hypercapnic respiratory failure, the 180 day mortality rate was 33%. The complainant stated that this was a particularly ill group of patients and that the 180 day mortality rate was not 33%. The complainant had not stated whether he considered the 180 day mortality rate to be more or less than 33%. The Panel noted that Seneff *et al* reported that in a different patient group (those aged 65 years or older admitted to intensive care primarily with an acute exacerbation of COPD), 180 day mortality was 47%. The Panel noted the difference in 180 day mortality rates between the two groups and also that there was no way of comparing the COPD severity of the two groups. The Panel noted Novartis' submission that the 47% 180 day mortality rate in Seneff *et al* indicated that the claim in question was not exaggerated. The Panel noted however that the complaint was not one of exaggeration but of accuracy. Given the difference in the 180 day mortality rate reported in the literature, the Panel considered that the unqualified, unconditional claim at issue 'The 180 day mortality rate following a COPD exacerbation is 33%' was misleading. It implied that the 180 day mortality in any patient following a COPD exacerbation had been categorically proven to be 33% which was not so. In that regard the Panel considered that the claim could not be substantiated. Breaches of Clause 7.2 and 7.4 were ruled.

The Panel noted that the second half of the claim at issue, 'and therefore reductions in exacerbations can reduce mortality rates', was not referenced. Novartis submitted that the claim reflected current medical opinion and was not linked to any specific treatment. The Panel did not accept Novartis' submission that the claim was not linked to any specific treatment. Given the data on the facing page about Seebri Breezhaler and exacerbations there was at the very least an inference that treatment with Seebri Breezhaler would have a positive impact on mortality. The Panel further noted Novartis's submission that no single study had successfully demonstrated that a specific treatment for COPD had decreased overall mortality. Halpin reviewed COPD treatment and noted that although the ISOLDE study showed that inhaled fluticasone significantly reduced the rate of exacerbations, a post hoc analysis only showed a non-significant trend towards improved survival (Briggs *et al* 2006). However, in the TORCH study, although fluticasone reduced the rate of exacerbation, it did not show a reduction in all-cause mortality at 3 years vs placebo (Calverley *et al* 2007). Halpin also reported that tiotropium had been shown to reduce exacerbation frequency and that a post hoc analysis suggested that it might reduce the rate of decline of FEV1; if this was a real effect then it might have an effect on mortality. Halpin further reported the benefits to COPD patients in preventing exacerbations of adding inhaled corticosteroids to long-acting B2-agonists but the studies cited did not link this benefit to a decrease in mortality. Conversely, other studies which examined the impact of adding inhaled corticosteroids to bronchodilator therapy did not link the reduced risk of death with a reduced rate of exacerbation. Halpin acknowledged that the studies reviewed, with the exception of the TORCH study, were not designed to assess mortality rates – most were underpowered as death was an uncommon event. The Panel noted that the complainant had referred to two studies (Tashkin *et al* and Vogelmeier *et al*) neither of which had been cited by Halpin. The complainant noted that these studies showed that although tiotropium was possibly more effective than long-acting B2-agonists, in a study that compared time to first exacerbation of COPD, a four year study in which mortality was a secondary endpoint failed to demonstrate a benefit from the use of tiotropium.

Overall, the Panel considered that although the strong claim that 'reductions in exacerbations can reduce mortality rates' appeared to be self-evident, it did not reflect the balance of the data. The claim implied that reducing COPD exacerbations with treatment had been unequivocally shown to reduce mortality rates which was not so. The Panel considered that the claim was misleading as alleged and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that page 7, which immediately followed and was opposite the claims considered above, was headed 'Glycopyrronium and exacerbations'. The page featured a table which detailed the secondary outcomes from the GLOW-1 study (glycopyrronium vs placebo) and the GLOW-2 study (glycopyrronium vs tiotropium). In both studies the primary efficacy endpoint was trough FEV1 at 12 weeks. Above the table was an explanation that a secondary objective of the two studies was to explore the first COPD exacerbation with glycopyrronium vs placebo over 26 weeks (GLOW-1) and 52 weeks (GLOW-2). Exploratory endpoints for GLOW-2 also included measuring the effect of glycopyrronium vs tiotropium in time to first exacerbation. The table, however, had two columns headed 'Endpoint' and 'Result' and so the secondary nature of the endpoints detailed within was not immediately obvious. The Panel considered that the explanation of the endpoints above the table was not prominent and thus was insufficient in this

regard. The Panel considered that the presentation of the data was not sufficiently complete to allow the reader to appreciate its statistical significance. The Panel considered that the table was misleading in that regard. A breach of Clause 7.2 was ruled.

Given its rulings above, the Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

Complaint received **18 March 2013**

Case completed **1 May 2013**
