HOSPITAL CONSULTANT v WARNER CHILCOTT

Promotion of Asacol

A consultant physician and gastroenterologist complained about a leavepiece for Asacol (modified release (MR) mesalazine) issued by Warner Chilcott headed 'For moderately active ulcerative colitis (UC): Back to normal everyday life, sooner – Asacol 4.8g/day vs mesalazine 2.4g/day'. The leavepiece had been used with gastroenterologists and related health professionals. On opening the front flap, the right hand page featured the claim at issue, 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location'. Cited in support of the claim were three clinical trials assessing the safety and clinical efficacy of a new dose (ASCEND) of mesalazine (ASCEND I, II and III) (Hanauer *et al* 2007; Hanauer *et al* 2005; Sandborn *et al* 2009). Warner Chilcott submitted that these studies constituted the phase three clinical programme.

The complainant stated that the claim implied that using Asacol 800mg MR tablets, there would be a treatment success of 72%, either with complete remission or clinical response. The complainant alleged that this was misleading as the ASCEND studies reported remission rates of less than 20%.

The detailed response from Warner Chilcott is given below.

The Panel noted that treatment success was defined in the three ASCEND studies as either a complete response (remission) or a clinical or partial response (improvement) to treatment from baseline at week 6. In ASCEND I, 72% of patients with moderate disease treated with Asacol 4.8g/day, achieved overall improvement. It was not reported how many of these patients had a complete response to therapy. In ASCEND II, 71.8% of patients with moderate disease treated with Asacol 4.8g/day were classified as having overall improvement; 20.2% achieved complete remission and 51.6% had a clinical response to therapy. At week 6 in the ASCEND III study 70.2% 273/389 of patients receiving Asacol 4.8g/day achieved treatment success; complete and partial response rates were 2.6% and 67.6% respectively.

The Panel noted that the implication of the ASCEND data was that in approximately 30% of patients, treatment with Asacol 4.8g/day resulted in neither remission nor improvement, as defined by the studies.

The Panel noted that the front cover of the leavepiece referred to 'Back to normal everyday life, sooner'. The claim at issue was 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location'. In the Panel's view most readers would assume that 'treatment success' meant a complete response to therapy ie remission. This was not so. The Panel did not consider that the qualification '(complete remission or clinical response to therapy)' was sufficiently detailed such as to allow readers to understand the significance of the data. Results from the ASCEND studies suggested that prescribers were more likely to see patients with a partial response, or neither remission nor improvement as defined in the studies, to Asacol 4.8g/day therapy than those in remission. The Panel considered that the claim was misleading and exaggerated; the data did not substantiate the impression given by the claim. Breaches of the Code were ruled.

Upon appeal by Warner Chilcott the Appeal Board noted that the ASCEND studies were conducted to support the registration of Asacol 800mg MR tablets. The primary endpoint in the study programme was the proportion of patients who achieved 'treatment success' at week 6. 'Treatment success' was a composite endpoint defined in ASCEND I and II as either complete remission or clinical response to therapy. In ASCEND III it was defined as either a complete response (remission) or a partial response (improvement) to treatment. The Appeal Board noted that the reference to treatment success in the claim 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location' was immediately followed by the definition '(complete remission or clinical response to therapy)'.

The Appeal Board noted that the ASCEND studies used the terms 'treatment success' and 'overall improvement' interchangeably. The Appeal Board noted that the leavepiece was intended for use with gastroenterologists and related health professionals. In the Appeal Board's view the term 'treatment success' in the context of ulcerative colitis, although defined and derived from the ASCEND studies, would, nonetheless, be understood by the specialists to whom the leavepiece was aimed. The claim included a definition of 'treatment success'.

The Appeal Board did not consider that the claim at issue was misleading or exaggerated as alleged and ruled no breaches of the Code. The Appeal Board considered that the claim did not imply that 72% of patients treated with Asacol 4.8g/day would achieve complete remission; rather that 72% of patients would achieve either a partial or complete response to therapy. The claim therefore could be

substantiated by the ASCEND studies. No breach of the Code was ruled. The appeal on all points was successful.

A consultant physician and gastroenterologist complained about a six page, gate-fold leavepiece for Asacol (modified release (MR) mesalazine) (ref AS8538) issued by Warner Chilcott. The leavepiece was headed 'For moderately active ulcerative colitis (UC): Back to normal everyday life, sooner – Asacol 4.8g/day vs mesalazine 2.4g/day'. On opening the front flap, the right hand page featured the claim 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location'. Cited in support of the claim were three clinical trials assessing the safety and clinical efficacy of a new dose (ASCEND) of mesalazine (ASCEND I, II and III) (Hanauer *et al* 2007; Hanauer *et al* 2005; Sandborn *et al* 2009). Warner Chilcott submitted that these studies constituted the phase three clinical programme.

Warner Chilcott representatives had used the leavepiece with gastroenterologists and related health professionals, such as irritable bowel disease nurses, with an interest in gastroenterology and ulcerative colitis.

COMPLAINT

The complainant stated that within the leavepiece, there was an implication that using Asacol 800mg MR tablets, there would be a treatment success of 72%, either with complete remission or clinical response. The complainant alleged that this was misleading as the actual remission rates reported in the ASCEND studies I, II and III, were less than 20%.

The Authority asked Warner Chilcott to respond in relation to Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Warner Chilcott stated that within the ASCEND programme the primary endpoint was the proportion of patients in each treatment group which achieved treatment success at six weeks. Overall improvement was a term synonymous with treatment success, as described in the clinical papers. Treatment success was defined as either complete remission or clinical response to therapy, as detailed in ASCEND I, II and III (Hanauer *et al* 2007 and 2005 and Sandborn *et al*).

For patients with moderately active ulcerative colitis receiving Asacol 4.8g/day, dosed with the 800mg MR, 72% (55/76), 71.8% (89/124) and 70.2% (273/389) of patients achieved treatment success at week 6, in ASCEND I, II and III, respectively.

Warner Chilcott submitted that the claim reflected the findings presented in the ASCEND papers and as such it considered the claim was accurate, fair and balanced and consistent with Clause 7.2. The claim was substantiable; citation and reference details were included in the leavepiece. Warner Chilcott thus considered the claim was consistent with Clause 7.4. Treatment success was demonstrated across all three studies in the proportion presented in the claim and had not been exaggerated. As such, Warner Chilcott considered this to only encourage rational use of the medicine, thus upholding Clause 7.10.

In response to a request for further information, Warner Chilcott provided copies of a poster and of an abstract by Sandborn *et al* (2006).

PANEL RULING

The Panel noted that treatment success was defined in the three ASCEND studies as either a complete response (remission) or a clinical or partial response (improvement) to treatment from baseline at week 6. Each study defined the parameters used to assess the clinical response or partial response.

The ASCEND I trial studied patients with mild to moderate active ulcerative colitis. In patients with moderate disease treated with Asacol 4.8g/day, 72% (55/76) achieved overall improvement. It was not reported how many of these patients had a complete response to therapy.

ASCEND II only included those with moderate disease and of those treated with Asacol 4.8g/day, 71.8% (89/124) were classified as having overall improvement; 25 patients (20.2%) achieved complete remission and 64 patients (51.6%) had a clinical response to therapy.

The ASCEND III trial also only included patients with moderate ulcerative colitis. At week six, 70.2% (273/389) of patients receiving Asacol 4.8g/day achieved treatment success; complete and partial response rates were 2.6% and 67.6% respectively.

The Panel noted that the implication of the ASCEND data was that in approximately 30% of patients, treatment with Asacol 4.8g/day resulted in neither remission nor improvement, as defined by the studies.

The Panel noted that the front cover of the leavepiece referred to 'Back to normal everyday life, sooner'. The claim at issue was 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location'. In the Panel's view most readers would assume that 'treatment success' meant a complete response to therapy ie remission. This was not so. The Panel did not consider that the qualification '(complete remission or clinical response to therapy)' was sufficiently detailed such as to allow readers to understand the significance of the data. Results from the ASCEND studies suggested that prescribers were more likely to see patients with a partial response, or neither remission nor improvement as defined in the studies, to Asacol 4.8g/day therapy than those in remission. The Panel considered that the claim was

misleading and exaggerated. Breaches of Clauses 7.2 and 7.10 were ruled. The Panel did not consider that the data was such as to substantiate the impression given by the claim. A breach of Clause 7.4 was ruled.

APPEAL BY WARNER CHILCOTT

Warner Chilcott considered that the claim at issue was fully substantiated by reference to an approved, clinically meaningful endpoint of the pivotal clinical studies that supported Asacol. Furthermore, it was not misleading or exaggerated, as the claim did not refer only to complete remission rates, nor did the claim imply that 72% of patients achieved complete remission. Warner Chilcott thus denied breaches of Clauses 7.2, 7.4 and 7.10.

Warner Chilcott explained that the claim at issue was developed from the three ASCEND studies, which constituted the pivotal, phase three, clinical trial programme for Asacol 800mg MR tablets; the studies had been published in peer reviewed journals (Hanauer *et al* 2007 and 2005 and Sandborn *et al*).

Within the ASCEND clinical programme the primary endpoint was the proportion of patients in each treatment group that achieved treatment success at six weeks. This endpoint, which denoted clinical improvement, was clinically relevant and had been accepted by the Medicines and Healthcare products Regulatory Agency (MHRA)/Food and Drug Administration (FDA) when they granted Asacol 800mg MR tablets a marketing authorization. Treatment success, as described in the clinical papers and trial protocol, constituted 'complete remission or clinical response' to therapy. Treatment success was used synonymously with the term overall improvement in the ASCEND studies.

The ASCEND programme demonstrated the efficacy of Asacol 800mg MR tablets (4.8g/day) in patients with moderately active ulcerative colitis; 72% (55/76), 71.8% (89/124) and 70.2% (273/389) patients achieved the primary endpoint of treatment success (complete remission or clinical response to therapy) at week 6, in ASCEND I, II and III, respectively. These results fully reflected the details within the claim and therefore it was not in breach of Clause 7.2, 7.4 or 7.10.

Warner Chilcott submitted that the claim was in line with the studies and the Code; it had ensured that the meaning of treatment success was clear with the addition of a definition, as per the studies. Thus, in the leavepiece, 'treatment success' was immediately qualified by '(complete remission or clinical response to therapy)'.

The term 'treatment success' comprised patients who achieved either complete remission or a clinical response to therapy, as defined by the study protocol, and was accepted by the MHRA and FDA as a meaningful endpoint and measure to demonstrate the efficacy of Asacol 800mg MR tablets for moderately active ulcerative colitis. Thus patients in the ASCEND study programme had a positive, meaningful, successful treatment outcome ('treatment success') if they achieved complete remission of moderately active ulcerative colitis or demonstrated a clinical response to therapy, at six weeks of treatment:

- Complete remission: a complete resolution of ulcerative colitis signs and symptoms. Patients who achieved complete remission met the primary endpoint of treatment success.

- Clinical response to therapy: a positive change in signs and symptoms. In the ASCEND programme this constituted an improvement in some of the key clinical measures to assess activity of symptoms and severity of ulcerative colitis flare, from baseline at six weeks. 'Clinical response' was a well recognised and established term and did not mean 'remission'. Patients who achieved a clinical response to therapy met the primary endpoint of treatment success.

Therefore, in the ASCEND study programme up to 72% patients were considered as having treatment success, at six weeks, if they had achieved either complete remission or had demonstrated a clinical response to therapy.

In the claim, 'clinical response to therapy' was presented equally as one of two key parameters which comprised the overall treatment success measure used in the programme. The other component of which was remission. Thus it was clear that overall 'up to 72% patients achieving treatment success' comprised patients with either complete remission or clinical response to therapy. Therefore it was not reasonable to suggest that the claim implied 'remission', because 'clinical response to therapy' was equally presented within the claim, and thus was consistent with Clauses 7.2, 7.4 and 7.10.

Warner Chilcott noted that the Panel had referred to the front cover of the leavepiece and the claim 'Back to normal everyday life, sooner', which it linked to the claim at issue, and the assumption was made that 'most readers would assume that 'treatment success' meant a 'complete response'. In Case AUTH/2267/9/09 it was determined that the claim 'Back to normal everyday life, sooner', was not in breach of the Code, where the Panel stated that the implication was not that Asacol would return patients to a pre-ulcerative colitis state but was used to describe a patient returning to 'everyday activities'. The Panel also stated that it 'did not consider that 'normal' would be read as describing the patient's disease state'. In line with this ruling, Warner Chilcott considered that the impression created by the leavepiece now at issue was not that all patients would have a 'complete response to therapy, ie remission'.

Warner Chilcott submitted that the complainant appeared to have assumed that 'complete remission or clinical response to therapy' equated to 'remission'. If the claim had stated solely 'treatment success' without the qualifiers providing further definition, Warner Chilcott agreed that this could have misled the reader. Similarly, if the claim had stated 'treatment success (remission)' then this would have been incorrect and in breach of the Code.

Clinical response to therapy, a recognised and established term with health professionals, was sufficiently descriptive and did not require further explanation; it did not imply or mean complete remission. Warner Chilcott never made a claim for 'complete response'; this was an assumptive term introduced by the Panel.

When treatment success was stated in the leavepiece it was immediately followed and qualified by '(complete remission or clinical response to therapy)'. Warner Chilcott did not state or imply that treatment success would refer to, or only mean, those patients who achieved complete remission, and was therefore not in breach of the Code.

As stated by the Panel, 'Results from the ASCEND programme suggested that prescribers were more likely to see patients with a partial response, or neither remission nor improvement as defined in the studies, to Asacol 4.8g/day therapy than those in remission'. Indeed it was true that, based on the findings of the ASCEND studies, a physician was more likely to see patients with a partial response, ie a clinical response to therapy, and it was those very patients that were represented within the claim: '(complete remission or clinical response to therapy)'. Both the Panel and Warner Chilcott acknowledgement of the data, as noted above, concurred and the claim was neither misleading nor exaggerated and thus not in breach.

In summary, Warner Chilcott disagreed that the claim implied remission. As correctly stated by the Panel, 72% of patients with treatment success denoted those patients with either complete remission or clinical response to therapy; as was represented in the claim. The claim was technically correct, as substantiated by the approved and clinically relevant primary findings of the ASCEND clinical programme. As the claim was fully substantiated, Warner Chilcott denied a breach of Clause 7.4.

Warner Chilcott maintained that the claim was substantiated, was not exaggerated and provided the reader with enough information to make an informed prescribing decision; it was therefore not in breach of Clauses 7.2 and 7.10.

COMMENTS FROM THE COMPLAINANT

The complainant maintained that the claims could not be substantiated.

APPEAL BOARD RULING

The Appeal Board noted that the ASCEND studies were conducted to support the registration of Asacol 800mg MR tablets. The primary endpoint in the ASCEND study programme was the proportion of patients who achieved 'treatment success' at week 6. 'Treatment success' was a composite endpoint defined in ASCEND I and II as either complete remission or clinical response to therapy. ASCEND III defined treatment success as either a complete response (remission) or a partial response (improvement) to treatment. The Appeal Board noted that the reference to treatment success in the claim 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location' was immediately followed by the definition '(complete remission or clinical response to therapy)'.

The Appeal Board noted that all three ASCEND studies used the terms 'treatment success' and 'overall improvement' interchangeably. The Appeal Board noted that the leavepiece was intended for use with gastroenterologists and related health professionals, such as irritable bowel disease nurses with an interest in gastroenterology and ulcerative colitis. In that regard the Appeal Board noted that the leavepiece included advice on writing Asacol referral letters. In the Appeal Board's view the term 'treatment success' in the context of ulcerative colitis, although defined and derived from the ASCEND studies, would, nonetheless, be understood by the specialists to whom the leavepiece was aimed. The claim included a definition of 'treatment success'.

The Appeal Board did not consider that the claim at issue was misleading or exaggerated as alleged and ruled no breach of Clauses 7.2 and 7.10. The Appeal Board considered that the claim did not imply that 72% of patients treated with Asacol 4.8g/day would achieve complete remission; rather that 72% of patients would achieve either a partial or complete response to therapy. The claim therefore could be substantiated by the ASCEND studies. No breach of Clause 7.4 was ruled. The appeal on all points was successful.

Complaint received **6 April 2011**

Case completed **22 June 2011**