CASE AUTH/2238/6/09

PROCTER & GAMBLE v SHIRE

Promotion of Mezavant XL

Procter & Gamble Pharmaceuticals alleged that maintenance of remission claims for Mezavant XL (mesalazine prolonged release) by Shire Pharmaceuticals Limited were misleading. In two leavepieces Shire presented data for patients who were maintained in remission whilst taking Mezavant XL.

Procter & Gamble alleged that the leavepieces did not explain that 68% of patients who maintained 'complete remission' represented 68% of the approximately 40% or less of patients who achieved remission in the original trials (Kamm *et al* 2007 and Lichtenstein *et al*) and which included the placebo and comparator groups also in remission.

Procter & Gamble noted that page 1 of one of the leavepieces stated that 'Mezavant XL once-daily maintained clinical and endoscopic remission over 12 months' followed by 'Efficacy to induce complete remission'. Procter & Gamble alleged that these were separate endpoints in separate trials. Page 2 stated, 'Patients maintained the stringent endpoints of complete remission' and was followed by the claim, '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12'. There was no indication of how many patients achieved remission and the reader could be mistaken for thinking that the 68% referred to patients who achieved and maintained remission.

Similarly in the second leavepiece, Procter & Gamble acknowledged that Shire had presented the percentage of patients reported by Kamm *et al* (2007) who achieved remission. However, whilst a footnote explained that the figures were from those patients who achieved remission in parent trials, it did not clearly connect the reader to the number of patients who achieved remission to put the figures into context.

The detailed response from Shire is given below.

The Panel noted that each leavepiece included on its front page 'Efficacy to induce complete remission' together with the tag line 'Discover complete remission'. Each included the claim '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12' followed by an asterisk which directed readers to the footnote 'Results in patients who achieved clinical and endoscopic remission in parent trials. These patients then entered into a 12 month maintenance study'. The claim was referenced to Kamm *et al* (2008).

In the parent studies (Lichtenstein *et al* and Kamm *et al* 2007) patients were treated for acute disease for up to 8 weeks. In the per-protocol group 100% of patients met the strict remission criteria at month 0 and these were maintained at month 12 in 67.8% of patients in the once daily group. At 12 months 88.7% of patients in the per-protocol population had not relapsed.

One of the leavepieces included the data from one of the parent studies (Kamm *et al* 2007) showing that 40.5% of patients taking 2.4g/day once daily, n=84, achieved complete remission defined by clinical and endoscopic endpoints at week 8. In the other parent study, Lichtenstein *et al*, 34.1% of patients taking 2.4g/day twice daily, n=88, achieved clinical and endoscopic remission after eight weeks of treatment.

The Panel considered that the leavepieces were not sufficiently clear about the basis of the data from Kamm *et al* (2008) ie that the per-protocol patients in the maintenance study were the minority of patients from the acute studies who had achieved complete remission. The Panel considered that the way the data was presented, together with other claims about the induction or achievement of remission, would lead many readers to assume that Mezavant XL induced and maintained remission in 68% of patients which was not so.

The Panel did not consider that the claim at issue '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12' in the context of the leavepieces was sufficiently clear that Kamm *et al* (2008) measured maintenance of remission and not induction of remission. Although a footnote gave some information as to the basis of the study, the supplementary information to the Code stated that claims must be capable of standing alone and that they should not, in general, be qualified by the use of footnotes and the like. The Panel considered that each leavepiece was misleading as to the basis of the Kamm *et al* (2008) data as alleged. Thus the Panel ruled each in breach of the Code.

Procter & Gamble Pharmaceuticals UK Limited complained about the promotion of Mezavant XL (mesalazine prolonged release) by Shire Pharmaceuticals Limited. Inter-company dialogue had been unsuccessful.

Mezavant XL was indicated for the induction of clinical and endoscopic remission in patients with mild to moderate active ulcerative colitis. It was also indicated for maintenance of remission.

COMPLAINT

Procter & Gamble noted that patients who were treated with Mezavant XL for 8 weeks to induce remission (Kamm *et al* 2007 and Lichtenstein *et al*) were entered into a third trial (Kamm *et al* 2008) to determine the number of patients who were maintained in remission over 12 months. Patients who completed the 8 week trials reported by Kamm *et al* (2007) and Lichtenstein *et al* but who were not in remission, could enter an 8 week extension and if they were then in remission, could be recruited into the maintenance study. This was further complicated by the additional enrolment of patients who did not quite meet the strict clinical and endoscopic remission endpoints but who were considered by their doctor to be well enough to be recruited. In leavepieces UK/MEZ/08/0195 and UK/MEZ/08/0203 Shire presented data for patients who were maintained in remission whilst taking Mezavant XL. The figures presented were 68% and 88%. Procter & Gamble alleged that the difference between these figures was due to stricter criteria to define remission in the group that achieved 68% versus 88%.

Procter & Gamble alleged that the leavepieces did not explain that 68% of patients who maintained 'complete remission' represented 68% of the proportion who achieved remission in the original trials (Kamm *et al* 2007 and Lichtenstein *et al*) and extension, ie 68% of the approximately 40% or less of patients who achieved remission and which included the placebo and comparator groups also in remission.

Procter & Gamble noted that page 1 of the leavepiece UK/MEZ/08/0195, stated that 'Mezavant XL once-daily maintained clinical and endoscopic remission over 12 months' followed by 'Efficacy to induce complete remission'. Procter & Gamble alleged that these were separate endpoints in separate trials. Page 2, whilst providing Shire's definition of 'complete remission' stated, 'Patients maintained the stringent endpoints of complete remission' and was followed by the claim, '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12'. There was no indication of how many patients achieved remission and the reader could be mistaken for thinking that the 68% referred to patients who achieved and maintained remission.

Similarly in leavepiece UK/MEZ/08/0203, Procter & Gamble acknowledged that Shire had presented the percentage of patients who achieved remission, albeit only those data reported by Kamm *et al* (2007) on page 4. However, whilst a footnote on page 5 explained that the 68% and 88% figures were from those patients who achieved remission in parent trials, it did not clearly connect the reader to the number of patients who achieved remission to put the 68% and 88% figures into context.

Procter & Gamble alleged that the presentation of these data in this way was misleading and in breach of Clause 7.2.

RESPONSE

Shire submitted that the exact nature of the complaint was not clear. It appeared that Procter & Gamble had suggested that Shire had misled prescribers by accurately describing the results of a maintenance of remission study. Shire denied that the presentation of information about the maintenance of remission study was misleading. The allegation appeared to arise out of Procter & Gamble's misunderstanding as to the nature of the clinical trial data used to support claims of maintenance of remission and the way studies in support of this indication were designed, executed and reported. The claims in question were based on a maintenance of remission study (Kamm *et al* 2008).

Shire submitted that in common with any maintenance of remission study, patients were required to comply with the entry criteria specified in the protocol. Since patients enrolled complied with the protocol definition of remission, it followed that those patients assessed at a later timepoint still in protocol-defined remission had experienced maintenance of remission. The only legitimate way to express such results was by a simple statistical comparison of the proportion in remission at the end of the study (68%) compared with those in remission at the start (100%). The same rationale applied to patients who were in remission at the start of the study and were found to be relapse-free at the end of the study (at 12 months, 88% were relapse-free, a less stringent clinical definition than clinical and endoscopic remission, as set out prospectively in the study protocol).

In each instance cited by Procter & Gamble, Shire noted that the data was presented on patients after 12 months' treatment in Kamm *et al* (2008) and the difference between the criteria for 68% patients maintained in remission and the criteria for the 88% who remained relapse-free was explained by the respective definitions of these measurements on both leavepieces. Furthermore the prominent labelling of the two different concepts drew the reader's attention to the fact that these were different concepts. As a result, Shire did not accept that the presentation of the maintenance of remission and relapse-free data in the leavepieces was confusing or misleading and that the differences in criteria were not adequately explained.

Shire submitted that because the maintenance study was a self-contained clinical trial with its own protocol and analysis plan, it was inappropriate of Procter & Gamble to suggest that the results of this study should be qualified in any way by the results of any other study which might or might not have fed patients into this specific maintenance study.

Concerning the other points raised, Shire agreed with Procter & Gamble's interpretation of the clinical study designs and was reassured that the company had understood these study designs correctly.

Shire had also considered the points raised by Procter & Gamble concerning patients' response to Mezavant XL in the acute studies (in which remission of active disease was induced) and their relevance to the long-term, 12 month study (in which remission of ulcerative colitis was maintained).

Shire submitted that clearly these two issues were completely unrelated. For the maintenance study, of all the patients who met the endoscopic and clinical criteria for remission at the start of this 12 month period (ie 100%, the per-protocol population), 68% of this group were still in remission after 12 months. (The study publication stated: 'In the "per-protocol" population in which, by definition, 100% of patients in both groups met the strict remission criteria at month 0, endoscopic and clinical remission were maintained at month 12 in 67.8% of the once-daily group…', Kamm *et al* 2008). The opposite was true of the acute studies at baseline. Although the maintenance study accepted patients from the acute studies, it was an entirely separate clinical study as Procter & Gamble acknowledged. The acute studies were different protocols, different patient populations with different aims and outcomes. The maintenance study only enrolled patients who met the strictly-defined clinical and endoscopic criteria for remission and were thus eligible for inclusion. Hence the acute studies from which the patients originated had no relevance to the complaint about the validity of the results for the maintenance study itself.

Having reviewed page 1 of the leavepiece (ref UK/MEZ/08/0195), Shire agreed that the claim 'Efficacy to induce complete remission' should not appear below 'Mezavant XL once-daily maintained clinical and endoscopic remission over 12 months'. Shire agreed with Procter & Gamble's assertion that these were separate endpoints in separate studies and as the leavepiece was communicating the maintenance of remission data, the claim 'Efficacy to induce complete remission' could be potentially confusing. Shire, however, noted that this complaint had not been specifically raised in inter-company correspondence.

In summary in relation to Procter & Gamble's remaining points, Shire submitted that it did not consider that the results from acute studies were relevant to the consideration of allegations about the presentation of the results from the maintenance of remission study. As Procter & Gamble clearly understood the separate nature of the various study designs, it was odd that it had suggested that these studies should be considered as forming some sort of continuum with the maintenance study. Shire thus denied a breach of Clause 7.2, save that the claim 'Efficacy to induce complete remission' should not have appeared below the maintenance data.

Shire wanted to correct the impression that all the points Procter & Gamble had complained of had been raised and discussed in detail in inter-company dialogue. As was evident from Procter & Gamble's correspondence of 6 and 29 April, as well as the final correspondence of 26 May, the company's complaints had been numerous and evolved over time. The predominant issue was not raised by Procter & Gamble until 29 April and then only as a subset of its main complaint that 'Presentation of the data to support the maintenance claims for Mezavant XL, 68% of patients remaining in 'complete remission' and 88% of patients being relapse free was misleading and in breach of Clause 7.2 of the Code'. Furthermore the complaint was not raised in the level of detail it had been presented to the Authority.

As was highlighted above, Procter & Gamble's complaint about the claim 'Efficacy to induce complete remission' had never been specifically raised in inter-company correspondence.

Shire confirmed that the claim 'Efficacy to induce complete remission' would be removed from the Mezavant XL leavepiece UK/MEZ/08/0195.

PANEL RULING

The Panel noted that Shire had agreed to cease use of a number of claims referring to complete remission in its promotional material including the leavepieces now at issue (UK/MEZ/08/0195 and UK/MEZ/08/0203).

The Panel noted that each leavepiece included on its front page 'Efficacy to induce complete remission' together with the tag line 'Discover complete remission'. Each included the claim '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12' followed by an asterisk which directed readers to the footnote 'Results in patients who achieved clinical and endoscopic remission in parent trials. These patients then entered into a 12 month maintenance study'. The claim was referenced to Kamm *et al* (2008).

In the parent studies (Lichtenstein *et al* and Kamm *et al* 2007) patients were treated for acute disease for up to 8 weeks. Both parties agreed that as well as including patients maintained in remission at the end of 8 weeks, patients not in remission at this point could be entered into an 8 week extension study and then if in remission could be entered into Kamm *et al* (2008). The position was further complicated in that although not defined by the protocol, patients who were not in strictly defined remission but deemed by their doctor to be well enough at the end of the parent studies or the 8 week extension phase could enter the randomised maintenance study. However the per-protocol population included only those patients who met the strict protocol defined criteria for remission. In the per-protocol group 100% of patients met the strict remission criteria at month 0 and these were maintained at month 12 in 67.8% of patients in the

once daily group. At 12 months 88.7% of patients in the per-protocol population had not relapsed.

One of the leavepieces (ref UK/MEZ/08/0203) included the data from one of the parent studies (Kamm *et al* 2007) showing that 40.5% of patients taking 2.4g/day once daily, n=84, achieved complete remission defined by clinical and endoscopic endpoints at week 8. In the other parent study, Lichtenstein *et al*, 34.1% of patients taking 2.4g/day twice daily, n=88, achieved clinical and endoscopic remission after eight weeks of treatment.

The Panel considered that the leavepieces were not sufficiently clear about the basis of the data from Kamm *et al* (2008) ie that the per-protocol patients in the maintenance study were the minority of patients from the acute studies who had achieved complete remission. The Panel considered that the way the data was presented, together with other claims about the induction or achievement of remission, would lead many readers to assume that Mezavant XL induced and maintained remission in 68% of patients which was not so.

The Panel did not consider that the claim at issue '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12' in the context of the leavepieces was sufficiently clear that Kamm *et al* (2008) measured maintenance of remission and not induction of remission. Although a footnote gave some information as to the basis of the study the supplementary information to Clause 7.2 stated that claims must be capable of standing alone and that they should not, in general, be qualified by the use of footnotes and the like. The Panel considered that each leavepiece was misleading as to the basis of the Kamm *et al* (2008) data as alleged. Thus the Panel ruled each in breach of Clause 7.2 of the Code.

Complaint received **8 June 2009**

Case completed **10 July 2009**