PROFESSOR OF CARDIOLOGY v MERCK SHARP & DOHME

Promotion of Cozaar

A professor of cardiology complained that a Cozaar (losartan) journal advertisement, issued by Merck Sharp & Dohme and headed 'Cozaar: The facts', did not refer to the warning regarding the use of losartan in patients with heart failure who were on a beta-blocker and strongly implied that losartan was widely indicated for patients aged 60 years and over with chronic heart failure where acetylcholine esterase (ACE) inhibitors were unsuitable. The advertisement did not refer to the specific warnings in the summary of product characteristics (SPC) for losartan: ie that 'The combination of losartan with a beta-blocker should be used with caution' (Section 4.4) and 'An increased mortality was observed in ELITE II in the small subgroup (22% of all HF [heart failure] patients) taking beta-blockers at baseline' (Section 5.1).

The complainant did not consider that prescribers reading the advertisement would be aware of this important caution. This was particularly important given that professional bodies and the Department of Health strongly encouraged increased prescribing of beta-blockers for this patient group.

The complainant considered it highly likely that the advertisement could lead to increased use of losartan specifically in the group for which there was a caution and increase mortality in this patient group. This was irresponsible and should be condemned. The advertisement was not only misleading but dangerous and should be withdrawn before it caused further damage.

The detailed response from Merck Sharp & Dohme is given below.

The Panel noted that the aim of the advertisement was to compare the licensed indications of Cozaar with those of six other AII-antagonists (AIIAs). Above a table of data it was claimed that 'Cozaar is the only AIIA with four indications'. The table listed one of Cozaar's indications, not held by any of the other medicines, as 'Chronic heart failure in patients ≥ 60 years with an LVF ≤ 40% and where ACE inhibitors are unsuitable due to incompatability or contraindication'. This was a new indication. The Cozaar SPC (Section 4.1) did not qualify the indication in any way or refer the reader to any precautions or warnings about the concomitant use of Cozaar with beta-blockers. The Panel noted that the prescribing information in the advertisement at issue stated, under a heading of heart failure, 'Use with caution in… combination with a beta-blocker'.

The Panel considered that the advertisement was not inconsistent with the particulars listed in the Cozaar SPC and in that regard no breach of the Code was ruled. The Panel further did not consider that the advertisement was dangerous or misleading as alleged.

A professor of cardiology complained about the promotion of Cozaar (losartan) by Merck Sharp & Dohme Limited. The material at issue was an advertisement (ref 03-10CZR.09.GB.10159.Jc) which had appeared in, *inter alia*, the BMJ and was headed 'Cozaar: The facts'.

COMPLAINT

The complainant was concerned that the advertisement did not refer to the warning regarding the use of losartan in patients with heart failure who were on a beta-blocker. In fact the advertisement strongly implied that losartan was widely indicated for patients aged 60 years and over with chronic heart failure where acetylcholine esterase (ACE) inhibitors were unsuitable (due to incompatibility or contraindication). The advertisement did not refer to the specific warnings in the summary of product characteristics (SPC) for losartan:

- 'The combination of losartan with a beta-blocker should be used with caution' (Section 4.4)
- 'An increased mortality was observed in ELITE II in the small subgroup (22% of all HF [heart failure] patients) taking beta-blockers at baseline' (Section 5.1).

The complainant did not consider that prescribers reading the advertisement would be aware of this important caution. This was particularly important given that the professional bodies (including the British Society for Heart Failure, and the European Society of Cardiology) and the Department of Health (through the new quality outcome framework (QOF) target for beta-blockers for patients with heart failure) strongly encouraged increased prescribing of beta-blockers for this patient group.

The complainant considered it highly likely that the advertisement could lead to increased use of losartan specifically in the group for which there was a caution, and in fact could cause increased mortality in this patient group. This was irresponsible and should be condemned. The advertisement was not only misleading but dangerous, and might cost lives. It was very important that it was withdrawn before it caused further damage.

When writing to Merck Sharp & Dohme, the

Authority asked it to respond in relation to Clauses 2, 3.2, 7.2 and 9.1 of the Code.

RESPONSE

Merck Sharp & Dohme denied any breach of the Code. Section 4.1, Indications, of the Cozaar SPC included the following:

> 'Treatment of chronic heart failure (in patients ≥60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤40% and should be stabilised under the treatment of the chronic heart failure.'

There was no qualification on the use of Cozaar in heart failure in Section 4.3 Contraindications. Section 4.4, Special warnings and precautions for use, included the following statement:

> 'The combination of losartan with a beta-blocker should be used with caution (see section 5.1).'

In Section 5.1, Pharmacodynamic properties, it stated:

> 'An increased mortality was observed in ELITE II in the small subgroup (22% of all HF patients) taking beta-blockers at baseline.'

The ELITE II report (Pitt *et al*, 2000) referred to a difference in mortality found in patients receiving losartan and beta-blockers, one of many subsets of several endpoints analysed. In the small numbers involved it was not possible to assess the statistical significance of this finding and the authors commented in the discussion section of the report:

> 'The results on total mortality in ELITE II were generally consistent across subsets, based on predefined baseline characteristics. The on-treatment analysis gave similar results to that by intention to treat. The subsets of patients did not generally differ significantly in effect of losartan and captopril apart from those who were taking beta-blockers at randomisation (22% of the population). This difference was not seen if use was based on concomitant treatment with beta-blockers during the study. Patients on losartan and captopril also taking beta-blockers did better than most patients not on such treatment at randomisation, which is consistent with data from studies supporting a benefit of beta-blockers in such a population. The interaction between treatment effect and baseline beta-blocker use should be interpreted with caution given the small number of patients receiving these drugs and potential bias related to the reasons for administering these agents.'

Merck Sharp & Dohme submitted that in the context of the Cozaar licence in heart failure, it interpreted these findings as follows:

- All patients in the study were randomised to captopril, an ACE-inhibitor, or Cozaar
- A small number of these patients were already on a beta-blocker at the time of study randomisation
- In this subset of patients there was an apparent increase in survival rate in those randomised to captopril
- This was not assessable statistically because of the small numbers involved
- The licensed heart failure indication for Cozaar was restricted to use in those patients in whom treatment with ACE inhibitors is not considered suitable due to incompatibility… or contraindication, ie where ACE-inhibitors were no longer a treatment option
- Therefore these results need to be interpreted cautiously in relation to use in this indication

In the light of the overall study results and the authors' comments the regulatory authorities decided, during the pan-European harmonisation of the SPC that led to the granting of a congestive heart failure indication, to include a warning to use losartan with caution with concomitant beta-blockers in Section 4.4 of the SPC and that a more prominent site within the SPC was not necessary. For similar reasons the company also considered that this warning was appropriately covered by a mention in the prescribing information in advertisements of this sort and that a more prominent position was unnecessary.

Following the grant of the heart failure indication, the advertisement at issue was produced as a summary of the product's indications in a general-interest journal.

In this context, Merck Sharp & Dohme did not consider it either normal or necessary to include precautions from Section 4.4 of the SPC in the main body of promotional material. The company was certain that there was no precedent for a demand that it should give more prominence to the beta-blocker caution on use in heart failure. Proper reference was included in the prescribing information in accordance with the requirements of the Code.

Looking at other SPCs for angiotensin-II antagonists (AIIAs), Merck Sharp & Dohme noted that Section 4.4 of the Amias SPC included a warning on use in heart failure with concomitant ACE-inhibitors; Section 4.4 of the Diovan SPC cautioned careful monitoring in post-myocardial infarction patients; close monitoring of patients at risk from hyperkalaemia was recommended in Section 4.4 of the SPCs for Approvel, Olmetec and Micardis. As far

as Merck Sharp & Dohme knew, none of these warnings were mentioned in promotional copy for these medicines other than in the prescribing information.

To summarise, Merck Sharp & Dohme considered that there was no reason for it to feature the warning to use losartan with care in patients receiving concomitant beta-blockers more prominently than it currently did because:

- The warning on use in heart failure was already mentioned in the prescribing information and the user advised to consult the SPC before use
- There was no precedent for a suggestion that warnings of this sort should be given more prominence in promotional material than their current site in the prescribing information

For the above reasons Merck Sharp & Dohme concluded that the advertisement at issue was neither misleading nor unsafe and that it complied with the Code and the company denied breaches of Clauses 2, 3.2, 7.2 and 9.1.

PANEL RULING

The Panel noted that the aim of the advertisement was to compare the licensed indications of Cozaar with those of six other AIIAs. Above a table of data it was claimed that 'Cozaar is the only AIIA with four indications'. The table listed one of Cozaar's indications, not held by any of the other medicines, as 'Chronic heart failure in patients ≥ 60 years with an LVF ≤ 40% and where ACE inhibitors are unsuitable due to incompatability or contraindication'. This was a new indication. Section 4.1, Therapeutic indications, in the Cozaar SPC did not qualify the indication in any way or refer the reader to any precautions or warnings about the concomitant use of Cozaar with beta-blockers. The Panel noted that the prescribing information in the advertisement at issue stated, under a heading of heart failure, 'Use with caution in… combination with a beta-blocker'.

The Panel considered that the advertisement was not inconsistent with the particulars listed in the Cozaar SPC and in that regard no breach of Clause 3.2 was ruled. The Panel further did not consider that the advertisement was dangerous or misleading as alleged. No breach of Clause 7.2 was ruled. Given these rulings the Panel also ruled no breach of Clauses 9.1 and 2 as it considered that high standards had been maintained and the industry had not been brought into disrepute.

Complaint received **15 April 2009**

Case completed **22 May 2009**