CASE AUTH/2212/3/09

TAKEDA v MERCK SHARP & DOHME

Promotion of Cozaar

Takeda complained about a Cozaar (losartan) advertisement issued by Merck Sharp & Dohme. The advertisement, *inter alia*, compared the antihypertensive efficacy of Cozaar (losartan) with other angiotensin II antagonists (AIIA) stating that 'Losartan is as effective as other leading AIIAs and gives 24-hour blood pressure control' referenced to a meta-analysis by Conlin *et al* (2000) and to Baguet *et al* (2007). Beneath the claim the weighted average reduction in diastolic blood pressure from 43 published, double-blind, randomised, controlled trials was given in a table for losartan (50-100mg), candesartan (8-16mg) (Takeda's product Amias), valsartan (80-160mg) and irbesartan (150-500mg).

Takeda was concerned about the presentation of data from Conlin *et al* and its use to substantiate the claim 'Losartan is as effective as other leading AIIAs …'.

Takeda alleged that readers were unable to understand the clinical relevance of the data presented as the dose ranges cited for the four AIIAs were not like for like. Readers were unable to draw appropriate and accurate conclusions from the information, or form their own opinion of the therapeutic value of each of the medicines. Takeda detailed what it considered were inconsistencies in the stated doses and noted that readers could not be expected to know the full range of licensed doses for every AIIA and which doses were comparable (eg which was the usual maintenance dose or maximum dose for each).

Further, Takeda alleged that Conlin *et al* was out-of-date and did not reflect the current balance of evidence or support the claim in question. Conlin *et al* only included pre October 1998 studies by which time there had only been 4 head to head studies of losartan vs the other AIIAs.

Since then there had been a further 10 studies comparing losartan with either irbesartan or valsartan and a further 11 head to head studies that compared the effects of candesartan with losartan in patients with essential hypertension. The largest of these, two identical head to head studies demonstrated a significant blood pressure reduction advantage for candesartan compared with losartan. These data were submitted to the regulatory authorities and reflected in the candesartan summary of product characteristics (SPC).

With regard to hierarchy of evidence when comparing two medicines, head to head, randomised, controlled trials were more robust and meaningful than indirect comparisons such as Conlin *et al*. Individual head to head, randomised, controlled trials were only superseded with respect to hierarchy of evidence by a systematic review of all head to head, randomised, controlled trials that compared two medicines.

Furthermore, Conlin *et al* used to substantiate the claim concluded that there was no difference between the AIIAs this was not the same as stating they were as effective which could only be demonstrated in a study specifically designed to assess equivalence. The claim 'Losartan is as effective as other leading AIIAs …' was also all embracing. Losartan was as effective as other AIIAs at doing what? There were many ways to demonstrate the antihypertensive efficacy of medicines eg clinic blood pressure (BP), 24 hour ambulatory BP, diastolic and/or systolic BP, peak BP lowering effect, trough BP lowering effect, pulse pressure.

Takeda's second concern was that the quotation from the Cochrane review which appeared beneath the table of data 'there are no clinically meaningful BP lowering differences between available [AIIAs]' was taken in isolation, out of context and did not reflect the entirety of the review. For example, Cochrane *et al* stated:

'For many of the drugs, there are insufficient data for a full range of doses. Therefore it remains possible that there could be differences between some of the drugs. However, the data are most consistent with the near maximum BP lowering effect of each of the drugs being the same. *It would require head-to-head trials of different [AIIAs] at equivalent BP lowering doses to assess whether or not there are differences in the BP lowering efficacy between different drugs.* This review provides useful dose-response information for estimating equivalent doses …' (emphasis added by Takeda).

Takeda submitted that, when available, head to head studies should be considered when determining the balance of evidence. There was sufficient head to head evidence between losartan and several of the other AIIAs (including candesartan) that demonstrated that losartan was not as effective at lowering blood pressure as these other AIIAs. The use of the quotation from the Cochrane review and the claim 'Losartan is as effective as other leading AIIAs …' was an inaccurate, unbalanced and misleading representation of the full evidence base.

The Panel noted that the claim 'Losartan is as effective as other leading AIIAs and gives 24-hour

blood pressure control' appeared above a table which compared the blood pressure lowering effects of losartan, candesartan, valsartan and irbesartan as adapted from Conlin *et al*.

Conlin *et al* was a meta-analysis which compared the antihypertensive efficacy of losartan, valsartan, irbesartan and candesartan by evaluating 43 randomised, controlled trials. These trials compared AIIAs with placebo, other antihypertensive classes and direct head to head comparisons. The study concluded that the analysis suggested that AIIAs lowered blood pressure with similar efficacy when administered at their usual recommended doses for the treatment of hypertension. The study authors noted that four of the 42 studies were head to head studies where losartan was compared with valsartan, irbesartan and candesartan; these contributed less than 20% of all the available evidence on blood pressure efficacy. The Panel noted that little detail about the statistical analysis appeared in the published paper.

The Panel noted Takeda's comments about meta-analysis but considered that they were an established and valid methodology, particularly in the absence of head to head trials. Nonetheless, 'Losartan is as effective as other leading AIIAs …' was an unequivocal claim and readers might expect the supporting data to include head to head studies rather than a meta-analysis. There was no information in the advertisement that told readers that Conlin *et al* was a meta-analysis and thus that the data published in the advertisement were indirect comparisons. The Panel further noted the conclusion of Conlin *et al* was that the data suggested the AIIAs had similar efficacy.

The Panel noted each party's submission about the doses presented in the advertisement. The Panel noted that according to the valsartan and candesartan SPCs the maximum antihypertensive doses were 320mg and 32mg once daily respectively. These doses did not feature in the advertisement. The Panel noted Merck Sharp & Dohme's submission that candesartan 32mg currently represented less than 5% of total candesartan volume prescribed in the UK. Merck Sharp & Dohme had not submitted what percentage of patients received the maximum dose of losartan, which was included in the Conlin *et al* meta-analysis. Conlin *et al* stated that some of the four published studies in which losartan had been compared directly with valsartan, irbesartan and candesartan had suggested differences in efficacy or responder rates but that the results of the present meta-analysis showed no difference in blood pressure efficacy or responder rates. Conlin *et al* concluded that 'This analysis suggests that AIIA lower blood pressure with similar efficacy when administered at their *usual recommended doses'* (emphasis added).

The Panel considered that the information about the source of the data, the tentative nature of the conclusion and about the doses of the AIIAs ie starting, usual maintenance, maximum etc was not sufficiently complete and the material was misleading in this regard. Breaches of the Code were ruled.

The Panel noted that Conlin *et al* assessed data published up to October 1998. The Panel noted both parties' submissions about subsequent publication of head to head data. The Panel noted Merck Sharp & Dohme's submission that the findings of Conlin *et al* had been confirmed by subsequent meta-analyses; Cochrane (2008) and Baguet *et al*. The Cochrane meta-analysis only included clinical trials comparing AIIAs with placebo. Patients could have co-morbid conditions whereas the patient population in Conlin *et al* could have no concomitant disease. The Panel noted that whilst presentation of data from Conlin *et al* must comply with the Code it did not consider on the evidence presented that publication of subsequent relevant data rendered Conlin *et al* out-of-date and thus misleading as alleged. No breach of the Code was ruled on this narrow point.

The Panel did not consider the claim 'Losartan is as effective as other leading AIIAs …' all embracing as alleged. In the context in which it appeared it was clear that the claim referred to the lowering of blood pressure. No breach of the Code was ruled on this point.

The Panel noted that the Cochrane analysis stated that the evidence suggested that there were no clinically meaningful differences between available AIIAs for lowering blood pressure. The study authors noted there was a similarity in BP lowering effects at trough. However for many of the medicines there was insufficient data for a full range of doses and thus it was possible that there could be differences between some of the medicines. It would require head to head trials of different AIIAs at equivalent BP lowering doses to assess whether there were differences in the BP lowering efficacy of different medicines. The study authors also noted that the review provided useful dose response information for estimating equivalent doses and thus designing trials to compare different AIIAs. The Panel considered that the claim 'A new independent Cochrane review suggests that 'there were no clinically meaningful BP lowering differences between available [AIIAs]' inferred that it had been proven that there were no clinically meaningful blood pressure lowering differences between available AIIAs which was not so. The use of the word 'suggests' was insufficient to negate such an inference which was misleading and not a fair reflection of the Cochrane review as alleged. A breach of the Code was ruled.

Upon appeal by Merck Sharp & Dohme the Appeal Board noted that the authors of the Cochrane analysis stated that 'The evidence from this review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs]'.

The advertisement at issue, however, had only reproduced the second half of this statement as a quotation ie 'there are no clinically meaningful BP lowering differences between available [AIIAs]'. Although 'suggests' was included outside the quotation the Appeal Board considered that by not faithfully reproducing the authors' statement the quotation cited in the advertisement gave a more unequivocal overview of the Cochrane analysis than had been given by its authors.

The Appeal Board noted that the Code required claims, *inter alia*, to be based on an up-to-date evaluation of *all* the evidence and to reflect that evidence clearly. The Appeal Board recognised the value of meta-analysis but noted that only indirect comparisons of AIIAs were possible from the Cochrane analysis. Glenny *et al* (2005) had stated that when comparing competing interventions direct evidence from good quality, randomized, controlled trials should be used wherever possible. Without this evidence it might be necessary to look for indirect comparisons from randomized, controlled trials. The Appeal Board noted that there were some direct comparisons of the AIIAs and so in that regard it did not consider that the results of the Cochrane analysis could be viewed in isolation.

The Appeal Board noted that the Cochrane analysis had only included placebo controlled trials in which patients had been treated to target. In that regard the analysis had shown that all of the AIIAs were able to treat to target but beyond that it had not investigated any additional BP lowering efficacy. Conversely Bakris *et al* and Vidt *et al*, forced titrations of candesartan and losartan (Cozaar), showed that candesartan was more effective than losartan in lowering BP when both were administered once daily at maximum doses. Bakris *et al* reported that candesartan lowered mean sitting trough BP by 13.3/10.9mmHg compared with a mean reduction of 9.8/8.7mmHg by losartan at week 8 – a difference of 3.5/2.2mmHg. The difference between the two products with regard to mean sitting trough BP as reported by Vidt *et al* was 3.3/1.4mmHg.

The Appeal Board noted that small differences in BP lowering, such as reported by Bakris *et al* and Vidt *et al* could be clinically meaningful. In that regard the Appeal Board noted that a table of results in the Cochrane analysis showed similar differences between some of the AIIAs albeit by indirect comparison.

The Appeal Board considered the claim 'A new independent Cochrane review suggests that "there were no clinically meaningful BP lowering differences between available [AIIAs]"' inferred that it had been proven that there were no clinically meaningful blood pressure lowering differences between available AIIAs which was not so especially in light of the evidence from Bakris *et al* and Vidt *et al* which directly compared candesartan and losartan. The Appeal Board considered that the claim did not reflect the totality of the available evidence and it was misleading. The Appeal Board upheld the Panel's ruling of breaches of the Code. The appeal was unsuccessful.

Takeda UK Limited complained about an advertisement (ref 10-09 CZR.08.GB.10728.J) for Cozaar (losartan) issued by Merck Sharp & Dohme Limited which appeared in The Pharmaceutical Journal, 8 November. Inter-company dialogue had not resolved matters.

The advertisement was headed 'advertisement feature' followed by 'IMPORTANT: information that may impact PCT [primary care trust] finances'. The advertisement discussed the incidence of hypertension and that Cozaar would be the first angiotensin II antagonist (AIIA) to come off patent with an expected consequent price reduction and thus savings. The final section compared the antihypertensive efficacy of Cozaar with other AIIAs stating that 'Losartan is as effective as other leading AIIAs and gives 24-hour blood pressure control'. The claim that losartan was as effective as other leading AIIAs was referenced to a meta-analysis by Conlin *et al* (2000) and to Baguet *et al* (2007). Beneath the claim the weighted average reduction in diastolic blood pressure from 43 published, double-blind, randomised, controlled trials was given in a table for losartan (50-100mg), candesartan (8-16mg) (Takeda's product Amias), valsartan (80-160mg) and irbesartan (150-500mg*).

COMPLAINT

Takeda was concerned about the presentation of data from Conlin *et al* and its use to substantiate the claim 'Losartan is as effective as other leading AIIAs …'.

Takeda alleged that readers were unable to understand the clinical relevance of the information presented as the dose ranges included for the different AIIAs were not like for like. Unless this was made clear the readers were unable to draw appropriate and accurate conclusions from the information, or form their own opinion of the therapeutic value of each of the medicines. For example, the current licensed maximum doses for candesartan (32mg) and valsartan (320mg) were not included. The doses cited for losartan were the starting and usual maintenance dose (50mg) and maximum dose (100mg), whereas for candesartan and valsartan only the usual starting and maintenance doses were included. Readers could not be expected to know the full range of licensed doses for every AIIA and which doses were comparable (eg which was the usual maintenance dose or maximum dose for each). A breach of Clauses 7.2 and 7.3 was alleged.

Further, Takeda alleged that Conlin *et al* was out-of-date and did not reflect the current balance of evidence or support the claim 'Losartan is as

effective as other leading AIIAs …' and therefore there was a breach of Clauses 7.2 and 7.3.

Although published in 2000, Conlin *et al* only included studies that were published prior to October 1998. At the time, there had only been 4 head to head studies. Conlin *et al* stated:

'There have been four published studies in which losartan has been compared directly with valsartan, irbesartan and candesartan. Some of these trials have suggested differences in efficacy or responder rates between the agents tested. The results of the present meta-analysis show no difference in blood pressure efficacy or responder rates. Because these direct comparative studies contributed less than 20% of all available evidence on blood pressure efficacy, a meta-analysis of the sort provided in this paper might be regarded as a stronger basis for understanding the comparative efficacy of drugs in this class.'

When Conlin *et al* was published this might well have been correct. However, since October 1998 a significant number of head to head studies had compared the AIIAs, many of which had demonstrated differences in efficacy and therefore Takeda believed that the authors' assumption was no longer accurate. Specifically, there had been a further 10 studies comparing losartan with either irbesartan or valsartan and a further 11 head to head studies that compared the effects of candesartan with losartan in patients with essential hypertension (Takeda provided a list of candesartan vs losartan studies). The largest of these, two identical head to head studies comparing candesartan 32mg (the dose not included in Conlin *et al*) with losartan 100mg in 1,268 patients, demonstrated a significant reduction in trough systolic and diastolic blood pressure in favour of candesartan. These data were submitted to the regulatory authorities and included within the candesartan summary of product characteristics (SPC) 'The antihypertensive effect and tolerability of candesartan and losartan were compared in two randomised, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The trough blood pressure reduction (systolic/diastolic) was 13.1/10.5mmHg with candesartan cilexetil 32mg once daily and 10.0/8.7mmHg with losartan potassium 100mg once daily (difference in blood pressure reduction 3.1/1.8mmHg, $p<0.0001$).'

With regard to hierarchy of evidence when comparing two medicines, head to head, randomised, controlled trials were more robust and meaningful than an indirect comparison such as that used in Conlin *et al*. Individual head to head, randomised, controlled trials were only superseded with respect to hierarchy of evidence by a systematic review of all head to head, randomised, controlled trials that compared two medicines.

Furthermore, Conlin *et al* was used to substantiate the claim 'Losartan is as effective as other leading AIIAs …'. The analysis conducted by Conlin *et al* concluded that there was no difference between the AIIAs. This was not the same as stating they were as effective. This could only be demonstrated in a study specifically designed to assess equivalence. The claim 'Losartan is as effective as other leading AIIAs …' was also all embracing. Losartan was as effective as other AIIAs at doing what? There were many measurements that could be used to assess the antihypertensive efficacy of medicines eg clinic blood pressure (BP), 24 hour ambulatory BP, diastolic and/or systolic BP, peak BP lowering effect, trough BP lowering effect, pulse pressure.

Takeda stated its second concern was that the quotation from the Cochrane review which appeared beneath the table of data 'there are no clinically meaningful BP lowering differences between available [AIIAs]' was taken in isolation, out of context and did not reflect the entirety of the review. For example, the first section within the discussion section of the Cochrane Review was entitled 'Is there a difference in magnitude of BP lowering effect between individual drugs in the [AIIA] class?'. This section stated:

'For many of the drugs, there are insufficient data for a full range of doses. Therefore it remains possible that there could be differences between some of the drugs. However, the data are most consistent with the near maximum BP lowering effect of each of the drugs being the same. **It would require head-to-head trials of different [AIIAs] at equivalent BP lowering doses to assess whether or not there are differences in the BP lowering efficacy between different drugs.** This review provides useful dose-response information for estimating equivalent doses …' (emphasis added by Takeda).

Therefore, as discussed above when available, head to head studies between losartan and other AIIAs should be considered when determining the balance of evidence. Takeda believed that there was sufficient head to head evidence between losartan and several of the other AIIAs (including candesartan) that demonstrated that losartan was not as effective at lowering blood pressure as these other AIIAs. Takeda therefore believed that the use of the quotation from the Cochrane review and the claim 'Losartan is as effective as other leading AIIAs …' was an inaccurate, unbalanced and misleading representation of the full evidence base in breach of Clauses 7.2 and 7.3.

RESPONSE

Merck Sharp & Dohme noted that throughout inter-company dialogue and in the complaint Takeda had opposed Merck Sharp & Dohme's use of meta-analyses of randomised controlled trials to support claims of equivalence between AIIAs. In this context, Takeda had stated repeatedly that the company's use of meta-analysis data was inappropriate or outdated. This was not so.

Merck Sharp & Dohme considered that meta-analyses had a valid role in supporting promotional activities:

- They could compare large numbers of patients in a manner that head to head clinical trials could not.
- They provided an overview of all available data within the selection criteria (including unpublished data where available, thereby avoiding publication bias).
- Meta-analysis of the phase III data that formed part of a marketing authorization file often provided the best or only opportunity to generate 'placebo corrected' data, since placebo arms were rarely included in post-launch comparative studies.
- They were the preferred method of comparing products for medicines management groups, NHS pharmaceutical advisors and other key healthcare decision makers. In this instance, the use of such data to support a promotional item was particularly appropriate in that readers of The Pharmaceutical Journal included many in this group.

As Takeda had described it, the hierarchy of evidence ranked systemic reviews and meta-analysis as the highest levels of evidence. The National Institute for health and Clinical Excellence (NICE) ranked meta-analysis data as Class 1, ie a highest level of evidence. The European Medicines Evaluation Agency (EMEA) praised meta-analysis as a method of summarizing efficacy results and analysing less frequent safety issues.

The Authority had reviewed several complaints during the last year that had included consideration of promotional activities based on the results of meta-analyses, including two against the complainant. In each of these the Authority had not objected to the general principle of the use of such data to support claims; however, some complaints had been upheld where such data had been used inappropriately.

Conlin *et al* meta-analysis

Merck Sharp & Dohme had used Conlin *et al* in Cozaar promotional material for approximately 8 years. Takeda had not complained to the PMCPA about its use before.

Merck Sharp & Dohme explained that previous inter-company dialogue with Takeda about Merck Sharp & Dohme's use of Conlin *et al* had reached agreement. Merck Sharp & Dohme provided details including the agreement to an amended claim that Merck Sharp & Dohme could use in association with Conlin *et al*. The wording agreed with Takeda then was identical to that used in the item now at issue.

Takeda objected to Merck Sharp & Dohme's use of Conlin *et al*. In its opinion Merck Sharp & Dohme should not use Conlin *et al* to support a claim that 'Losartan is as effective as other leading AIIAs …' (in the context of BP lowering) on three grounds that. Merck Sharp & Dohme responded to these points in order:

1 The doses used in the study were not the full dose ranges for all of the comparators

Merck Sharp & Dohme agreed that not all currently available doses of all the current AIIAs were included in Conlin *et al*. This did not affect the company's ability to use the study in promotional material and the company believed that the PMCPA's findings in Merck Sharp & Dohme's recent complaint against Takeda supported this. Although Conlin *et al* did not include the 32mg dose of candesartan (which was not a licensed dose at the time of the analysis), subsequent meta-analyses, including the largest and most recent Cochrane review, had included it and come to the same conclusion. The more recent reports did not alter the validity, accuracy or context in which Conlin *et al* was used. In any case, the use of candesartan 32mg in the UK currently represented less than 5% of total candesartan volume prescribed in the UK (IMS UK BPI data, Jan 2009), and its clinical relevance was therefore limited.

Merck Sharp & Dohme submitted that the material had been transparent on the subject of the doses used in the meta-analysis; these were printed in full in the table describing results. Health professionals knew they should consult the relevant SPC before treating. In this context, sufficient information was provided for readers of The Pharmaceutical Journal to make up their minds about whether the claim was appropriate on the grounds of doses studied.

2 The study was out-of-date having been superseded by a number of head to head efficacy studies

To support its second point, Takeda stated it had supplied 11 head to head studies demonstrating superiority for candesartan over losartan in the management of hypertension whereas 12 references had been provided. Many of these studies were small; they frequently failed to reach statistical significance for all blood pressure variables (systolic and diastolic), and some were designed to assess endpoints other than blood pressure. Merck Sharp & Dohme did not believe that these invalidated the meta-analyses of 46 randomised, controlled trials in the Cochrane review (13,451 patients) or the 43 trials in Conlin *et al* (11,281 patients), or the claims it had based upon them.

The findings of Conlin *et al* had been confirmed by, and were in line with, subsequent meta-analyses (Cochrane (2008) and Baguet *et al*). The authors' findings remained valid and hence Merck Sharp & Dohme's continued use of this report in supporting promotional activities remained appropriate.

3 The study concluded that there was no difference between the AIIAs reviewed

Takeda had objected to the use of the phrase 'as effective as other leading AIIAs …' to describe the findings of a study which found no difference between the four comparators studied. This exact wording had been agreed during inter-company dialogue in November 2007; Merck Sharp & Dohme believed that the complaint was therefore inappropriate (having been the subject of agreement at inter-company dialogue) and meaningless. The meta-analyses found no meaningful difference in the BP lowering effectiveness of the four leading AIIAs. 'As effective as ….' seemed synonymous with that finding.

To summarise, whilst Merck Sharp & Dohme agreed that there might be times when it was not appropriate to use older scientific publications to support promotional activities, it believed it was permissible to do so where it could be shown to remain valid, for example where more recent publications continued to support the original conclusions. Merck Sharp & Dohme believed this to be true in its use of Conlin *et al*.

Cochrane Review

Takeda's complaint stated that Merck Sharp & Dohme had quoted the report in a manner that was out of context, and not reflective of the entirety of the review and noted that the review suggested that further studies were required to further evaluate the differences in efficacy.

Many of the points at issue had been covered above. Merck Sharp & Dohme remained unclear as to what Takeda's objection was to using the Cochrane Review in the way it had and to which area of the Code the alleged breaches referred.

The Cochrane Collaboration was acknowledged as the leading source of quality meta-analyses and its reports were used by regulatory authorities and medicines management groups, including NICE and the Scottish Intercollegiate Guidelines Network (SIGN), throughout the UK and the rest of the world. The Collaboration's review of AIIAs corroborated Conlin *et al* and added even more studies to the pool of patients reviewed by meta-analysis with the conclusion that there were no significant differences between the medicines in this class.

Takeda had complained that the report had been quoted out of context and in a way that did not reflect the entirety of the review.

The principal finding from the 2008 Cochrane review was crystal clear that 'The evidence from this review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs].'

Takeda's contention that meta-analysis was an invalid support for promotional activities once head to head, randomised, clinical trials were available was flawed. Merck Sharp & Dohme had already pointed out to Takeda in inter-company dialogue the largest study comparing candesartan and losartan included 332 and 322 patients respectively. The equivalent figures in the Cochrane Review were 762 and 2,134.

Merck Sharp & Dohme therefore did not agree that its use of the Cochrane Review was in breach of the Code. The conclusions supported a claim that 'Losartan is as effective as other leading AIIAs …' and Merck Sharp & Dohme considered that this type of review was an entirely valid comparison.

* * * * *

The Director noted Merck Sharp & Dohme's submission that the wording agreed with Takeda in inter-company dialogue 'Losartan is as effective as other leading AIIAs …' was identical to that used in the material at issue. The Director noted that agreement had been reached during inter-company dialogue in relation to an allegation and similar claim neither of which were at issue in the present case. The complaint was thus referred to the Panel for consideration.

PANEL RULING

The Panel noted that the claim 'Losartan is as effective as other leading AIIAs and gives 24-hour blood pressure control' appeared above a table which compared the weighted average reduction in diastolic blood pressure from 43 published double-blind, randomised, controlled trials of losartan (-10mmHg, 50-100mg, n=2,217) candesartan (-9.5mmHg, 8-16mg, n=593), valsartan (-9.6mmHg, 80-160mg, n=855) and irbesartan (-10.4mmHg, 150-500mg, n=610). The data was stated to be adapted from Conlin *et al*.

Conlin *et al* was a meta-analysis which compared the antihypertensive efficacy of losartan, valsartan, irbesartan and candesartan by evaluating 43 randomised, controlled trials. These trials compared AIIAs with placebo, other antihypertensive classes and direct head to head comparisons. The study concluded that the analysis suggested that AIIAs lowered blood pressure with similar efficacy when administered at their usual recommended doses for the treatment of hypertension. The study authors noted that four of the 42 studies were head to head studies where losartan was compared with valsartan, irbesartan and candesartan; these contributed less than 20% of all the available evidence on blood pressure efficacy. The Panel noted that little detail about the statistical analysis appeared in the published paper.

The Panel noted Takeda's comments about meta-analysis but considered that they were an established and valid methodology, particularly in the absence of head to head trials. Nonetheless,

'Losartan is as effective as other leading AIIAs …' was an unequivocal claim and readers might expect the supporting data to include head to head studies rather than a meta-analysis. There was no information in the advertisement that told readers that Conlin *et al* was a meta-analysis and thus that the data published in the advertisement were indirect comparisons. The Panel further noted the conclusion of Conlin *et al* was that the data *suggested* the AIIAs had similar efficacy.

The Panel noted each party's submission about the doses presented in the advertisement. The Panel noted that according to the valsartan and candesartan SPCs the maximum doses for treatment of hypertension were 320mg and 32mg once daily respectively. These doses did not feature in the advertisement. The Panel noted Merck Sharp & Dohme's submission that candesartan 32mg currently represented less than 5% of total candesartan volume prescribed in the UK. Merck Sharp & Dohme had not submitted what percentage of patients received the maximum dose of losartan, which was included in the Conlin *et al* meta-analysis. Conlin *et al* stated that some of the four published studies in which losartan had been compared directly with valsartan, irbesartan and candesartan had suggested differences in efficacy or responder rates but that the results of the present meta-analysis showed no difference in blood pressure efficacy or responder rates. Conlin *et al* concluded that 'This analysis **suggests** that AIIA lower blood pressure with similar efficacy when administered at their **usual recommended doses**' (emphasis added).

The Panel considered that the information about the source of the data, the tentative nature of the conclusion and about the doses of the AIIAs ie starting, usual maintenance, maximum etc was not sufficiently complete and the material was misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that Clause 7.2 required, *inter alia*, that claims had to be based on an up-to-date evaluation of all the evidence. Conlin *et al* assessed data published up to October 1998. The Panel noted both parties' submissions about subsequent publication of head to head data. The Panel noted Merck Sharp & Dohme's submission that the findings of Conlin *et al* had been confirmed by subsequent meta-analyses; Cochrane (2008) and Baguet *et al*. The Cochrane meta-analysis only included clinical trials comparing AIIAs with placebo. Patients could have co-morbid conditions whereas the patient population in Conlin *et al* could have no concomitant disease. The Panel noted that whilst presentation of data from Conlin *et al* must comply with the Code it did not consider on the evidence presented that publication of subsequent relevant data rendered Conlin *et al* out-of-date and thus misleading as alleged. No breach of Clauses 7.2 or 7.3 was ruled on this narrow point.

The Panel did not consider the claim 'Losartan is as effective as other leading AIIAs …' all embracing as alleged. In the context in which it appeared it was clear that the claim referred to the lowering of blood pressure. No breach of Clauses 7.2 and 7.3 was ruled on this point.

The Panel noted that the Cochrane analysis stated that the evidence suggested that there were no clinically meaningful differences between available AIIAs for lowering blood pressure. The study authors noted there was a similarity in BP lowering effects at trough. However for many of the medicines there was insufficient data for a full range of doses and thus it was possible that there could be differences between some of the medicines. It would require head to head trials of different AIIAs at equivalent BP lowering doses to assess whether there were differences in the BP lowering efficacy of different medicines. The study authors also noted that the review provided useful dose response information for estimating equivalent doses and thus designing trials to compare different AIIAs. The Panel considered that the claim 'A new independent Cochrane review suggests that 'there were no clinically meaningful BP lowering differences between available [AIIAs] 'inferred that it had been proven that there were no clinically meaningful blood pressure lowering differences between available AIIAs which was not so. The use of the word 'suggests' was insufficient to negate such an inference which was misleading and not a fair reflection of the Cochrane review as alleged. A breach of Clauses 7.2 and 7.3 was ruled.

During the consideration of this case the Panel noted Merck Sharp & Dohme's submission that sufficient information was provided such that readers could make up their minds about whether the claim was appropriate on the grounds of the doses studied. In the Panel's view this was unacceptable. Companies must always ensure that claims made for their medicines were appropriate. The Panel requested that Merck Sharp & Dohme be advised of its views in this regard.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme noted that this complaint was about how its journal advertisement had reported the Cochrane review of medicines in Cozaar's therapeutic class (AIIAs). The review analysed the results of 42 randomised, controlled clinical trials of seven AIIAs. The objective of the review was to quantify the dose-related systolic and/or diastolic BP lowering efficacy of AIIAs vs placebo in the treatment of primary hypertension.

Merck Sharp & Dohme submitted that in most therapy areas, relative efficacy was difficult to assess because of the number of head to head clinical studies, many performed in small numbers of subjects, some of which would show differences between comparators going either way, some of which would not. Meta-analysis was a valid tool for providing valid comparisons of therapeutic

outcomes. The Cochrane Collaboration was globally acknowledged by clinicians and medicines management groups for producing the highest quality of meta-analysis available to prescribing decision-makers. The claim 'A new independent Cochrane review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs] appeared in the advertisement at issue. As would be discussed later, what might not have been made evident to the Panel in its ruling was that the advertisement tracked the phraseology used in the review, including use of the word 'suggests'.

Takeda had referred to a particular quotation from the review's discussion section, but only used the second half of one paragraph in isolation. It would probably be appropriate to put the authors' opinions into context by quoting the entire paragraph: 'This review provides a reasonable amount of data to assess the trough BP lowering effect of 9 different [AIIAs]. When the different [AIIAs] are compared, there is a similarity in their BP lowering effects at trough. When the best estimate of the near maximal BP lowering efficacy of these 9 drugs is compared, they range from -6/-3 mm Hg to -10/-7 mm Hg. For many of the drugs, there are insufficient data for a full range of doses. Therefore it remains possible that there could be differences between some of the drugs. However, the data are most consistent with the near maximum BP lowering effect of each of the drugs being the same. It would require head-to-head trials of different [AIIAs] at equivalent BP lowering doses to assess whether or not there are differences in the BP lowering efficacy between different drugs. This review provides useful dose-response information for estimating equivalent doses and thus designing trials to compare different [AIIAs]'.

Merck Sharp & Dohme noted that this was the only instance in the report where comments were expressed by the authors that the review might not represent a comprehensive assessment of relative efficacy and the only mention of a need to perform head to head comparative studies.

Merck Sharp & Dohme submitted that on checking the full report for the authors' claim above that 'For many of the drugs, there are insufficient data for a full range of doses', it appeared that the following factors had influenced their concerns on this matter:

- Eprosartan had no reports relating to efficacy at the highest recommended daily dose, 800mg, although data were provided on unlicensed higher doses. Because of this the report concluded that 'the true near maximal BP lowering efficacy of eprosartan cannot be estimated'.

- Olmesartan, in the authors' opinion, had insufficient published data at doses above 20mg/day. Although data did exist, they concluded once again 'that the true near maximal BP lowering efficacy cannot be estimated'.

Merck Sharp & Dohme concluded was that the authors' comments about insufficient data across all licensed dose ranges of all AIIAs represented a, perhaps arguable, concern about insufficient data at the upper dose range only in just two of the seven AIIAs reviewed.

Elsewhere there were at least six references to equivalence in efficacy of the various AIIAs in controlling hypertension. These included the following sections of the review and the relevant quotation:

- Study abstract: main results. 'The data do not suggest that any one [AIIAs] is better or worse at lowering BP'
- Study abstract: authors' conclusions. 'The evidence from this review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs]
- Full report: plain language summary. 'No [AIIA] appears to be any better or worse than others in terms of blood pressure lowering ability'.
- Discussion: 'is there a difference in the magnitude of BP lowering effect between individual drugs in the [AIIA] class? When the different [AIIAs] are compared, there is a similarity in their BP lowering effects at trough'
- Authors' conclusions, implications for practice: specific findings (1). 'The data do not suggest that any one [AIIA] is better or worse than any other at lowering blood pressure when used at maximal recommended doses'
- Authors' conclusions, implications of these findings. See below.

The last of these, in authors' conclusions: implications of these findings included the most emphatic statement on how the review could best be interpreted: 'This systematic review provides the best available published evidence about the dose-related blood pressure lowering efficacy of [AIIAs] for the treatment of primary hypertension. These findings have the potential to change prescribing behaviour and drug funding policies around the world. The evidence from this review suggests that there are no clinically meaningful differences between available [AIIAs] for lowering blood pressure. Thus, substantial cost savings can be achieved by prescribing the least expensive [AIIA].'

Merck Sharp & Dohme submitted that these last comments, despite the use of the word 'suggests' but importantly included under a heading 'implication of these findings', put the authors' commitment to the review's findings into the context of a firm conclusion which was reflected in the advertisement in question.

The authors had listed the main reasons why they believed their review might not constitute a comprehensive review of class efficacy. These were covered in a specific section and included:

- **Publication bias.** The authors considered that there was selection of reports for publication with

a potential bias towards more favourable results. This was based on analysis of result scatter, a belief that much of the data used to support licensing was unpublished and lack of public domain data to support some dose schedules licensed in some countries.

- **Selection bias**. A common exclusion criterion in the studies reviewed was hypersensitivity to ACE-inhibitors. The authors believed this could indicate investigators having sufficient knowledge of the patients' treatment history to provide an opportunity to select patients more amenable to treatment.

- **Other sources**. The authors criticized the reports for generally providing insufficient information to reassure the reader that the methods used for randomizing patients and blinding subjects and/or treatments were adequate to eliminate selection or observer bias.

Merck Sharp & Dohme submitted that it was important to note that the authors' general conclusion in this section was that, although these factors might have resulted in an overall increase in apparent efficacy for the AIIA class, they were unlikely to have favoured any one agent within the class or invalidated the conclusion that the AIIAs had similar efficacy.

Merck Sharp & Dohme submitted that in pursuing this complaint against it, Takeda had only focussed on half of one paragraph in a 103 page document.

Merck Sharp & Dohme hoped that by noting all the points made by the Cochrane Collaboration authors, including the strength of their conclusions despite recognising potential bias, Merck Sharp & Dohme had provided context and reassurance that the claims made in relation to this meta-analysis were appropriate. The advertisement tracked the phraseology used in the review, including use of the word 'suggests'. In addition, it made clear that the comment was made in the context of that specific paper. Merck Sharp & Dohme submitted that the advertisement fairly represented the authors' conclusions from what was a robust and generally well respected report.

Merck Sharp & Dohme submitted that the Cochrane Collaboration made much of its independent status and scientific approach. Caveats referring to a need for further studies were not unusual in academic environments such as theirs. Three sentences in a 103 page report warning that further studies might be required needed to be put into context alongside five fairly unequivocal statements supporting a balanced final conclusion suggesting no meaningful differences within a class of medicine. Under the circumstances, Merck Sharp & Dohme submitted that it did not seem unreasonable to use the statement in a journal advertisement without fear of misleading readers.

For the reasons listed above, Merck Sharp & Dohme submitted that the use of this claim represented a measured, balanced, accurate and up-to-date assessment of the situation which did not mislead and was a fair reflection of the review's findings.

Merck Sharp & Dohme therefore disagreed that this aspect of the advertisement was in breach of Clauses 7.2 or 7.3 of the Code.

COMMENTS FROM TAKEDA

Takeda noted that the basis of its complaint which was upheld by the Panel in relation to the Cochrane review was two-fold:

Firstly, Takeda alleged that the claim in the advertisement relating to the Cochrane review, 'there are no clinically meaningful BP lowering differences between available [AIIAs]', was taken in isolation, out of context and did not reflect the entirety of the review.

Secondly, Takeda alleged that due to the availability of head to head studies comparing losartan with candesartan the use of the quotation relating to the Cochrane review (together with the other claim 'Losartan is as effective as other leading AIIAs') was an inaccurate, unbalanced and misleading representation of the full evidence base.

Takeda therefore alleged that the use of the claim 'A new independent Cochrane review suggests that "there are no clinically meaningful BP lowering differences between available [AIIAs]"' was in breach of Clauses 7.2 and 7.3.

As detailed by Merck Sharp & Dohme, the objective of the review was to quantify the dose-related systolic and/or diastolic BP lowering efficacy of the AIIAs vs placebo in the treatment of primary hypertension. It was not to formally assess whether differences existed between the AIIAs. The quotation used by Merck Sharp and Dohme; 'there are no clinically meaningful BP lowering differences between available [AIIAs], did not accurately reflect the objective of the review nor did it make it clear that the Cochrane review was an indirect meta-analysis which used placebo as the common comparator. When taken at face value with no further information on the methodology used in the Cochrane review, the reader could incorrectly conclude that the Cochrane Review was a direct comparison of the different AIIAs. Even if the results of the analysis were quoted accurately, it could still be misleading to use them promotionally without making the limitations of the analysis clear. This indirect analysis specifically excluded the direct head to head evidence available. By using it in isolation, Merck Sharp & Dohme had deliberately ignored the wealth of robust head to head data that existed. The authors were entitled to draw conclusions on their analysis alone. Merck Sharp & Dohme, however, not only had a responsibility to ensure that any promotional claims accurately reflected the paper being quoted, but also that it

accurately reflected the balance of evidence.

Takeda agreed with Merck Sharp & Dohme that when direct head to head clinical studies were not available, an indirect meta-analysis could be a valuable tool to help clinicians make prescribing decisions. However, when well conducted head to head randomised trials were available then this provided the most robust evidence. This was clearly the position of the Cochrane Collaboration and leading experts in the field. A recent article by the Cochrane Collaboration (Song *et al* 2009a,) assessed the validity of indirect meta-analysis and stated: 'Well designed randomised controlled trials (RCTs) generally provide the most valid evidence of relative efficacy of competing interventions, in which the possibility of selection bias is minimised (Kunz 2007). However, many competing interventions have not been compared directly (head-to-head) in RCTs. Even when different interventions have been directly compared in RCTs such direct evidence is often limited and insufficient. Lack of evidence from direct comparison between active interventions makes it difficult for clinicians to choose the most effective treatment for patients.'

The same authors had also published on the specific merits of head to head RCTs compared to indirect meta-analysis (Glenny *et al*, 2005). The introduction stated 'Well-designed randomised controlled trials (RCTs) generally provide the most reliable evidence of effectiveness as observed differences between the trial arms can, in general, be confidently attributed to differences in the treatment(s) being evaluated. However, in many areas, available trials may not have directly compared the specific treatments or regimens of interest. A common example is where there is a class of several drugs, each of which has been studied in placebo-controlled RCTs, but there are no trials (or very few) in which the drugs have been directly compared with each other'. The authors discussed this issue further in a recent publication on the methodological problems of using indirect comparisons for evaluating healthcare interventions published in the BMJ (Song *et al* 2009b).

Takeda alleged that the authors of the Cochrane Review on AIIAs were clear to reinforce that the findings of their indirect meta-analysis were not definitive and that; 'It would require head-to-head trials of different [AIIAs] at equivalent BP lowering doses to assess whether or not there are differences in the BP lowering efficacy between different drugs.'

As previously detailed Takeda noted that there were several well-conducted head to head randomised controlled trials involving over 3,000 patients directly comparing losartan with candesartan. The balance of this evidence was that losartan was not as effective as candesartan in lowering blood pressure. For example, the largest of these was the CLAIM study (Bakris *et al* 2001, Vidt *et al* 2001) programme which, as stated in the Amias SPC, compared the antihypertensive effect and tolerability of candesartan and losartan (both at their maximum licensed dose) in two identical randomised, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The trough blood pressure reduction was 13.1/10.5mmHg with candesartan and 10.0/8.7mmHg with losartan (difference of 3.1/1.8mmHg; $p<0.0001/p<0.0001$).

Takeda noted that the Cochrane review only included placebo-controlled studies which were usually conducted early in the development of a product and primarily for the purposes of registration. Subsequently, head to head studies directly comparing one medicine with another were then conducted. If an indirect meta-analysis of placebo controlled trials were the 'gold standard' for comparing one medicine with another then it would negate the need for head to head RCTs to be conducted

Takeda alleged that Merck Sharp and Dohme had implied that it had not provided the full detail of the Cochrane Review to the Panel. Although Takeda had referred to a particular part of the discussion had it provided the full Cochrane Review to the Panel for reference and review so that it could make a full assessment of the information. The most important limitation of this analysis was not mentioned by Merck Sharp & Dohme at any stage in its appeal, nor in the advertisement at issue. This analysis was indirect, and therefore excluded the extensive direct head to head evidence that existed comparing Losartan to several of the other AIIAs, including candesartan. Previous cases had reviewed and accepted the superiority data for a number of the AIIAs compared with losartan (eg Cases AUTH/1510/8/03, AUTH/1501/8/03). It would therefore seem at odds to agree that the direct evidence on the one hand showed superiority of other treatments, but that this indirect comparison justified a claim of no difference. This was not a criticism of the Cochrane review, merely an acknowledgement of the limitations of this kind of indirect analysis.

APPEAL BOARD RULING

The Appeal Board noted that the authors of the Cochrane analysis stated that 'The evidence from this review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs]'. The advertisement at issue, however, had only reproduced the second half of this statement as a quotation ie 'there are no clinically meaningful BP lowering differences between available [AIIAs]'. Although 'suggests' was included outside the quotation the Appeal Board considered that by not faithfully reproducing the authors' statement the quotation cited in the advertisement gave a more unequivocal overview of the Cochrane analysis than had been given by its authors.

The Appeal Board noted that the Code required

claims, *inter alia*, to be based on an up-to-date evaluation of *all* the evidence and to reflect that evidence clearly. The Appeal Board recognised the value of meta-analysis but noted that only indirect comparisons of AIIAs were possible from the Cochrane analysis. Glenny *et al* (2005) had stated that when comparing competing interventions direct evidence from good quality, randomized, controlled trials should be used wherever possible. Without this evidence it might be necessary to look for indirect comparisons from randomized, controlled trials. The Appeal Board noted that there were some direct comparisons of the AIIAs and so in that regard it did not consider that the results of the Cochrane analysis could be viewed in isolation.

The Appeal Board noted that the Cochrane analysis had only included placebo controlled clinical trials in which patients with primary hypertension had been treated to target with an AIIA. In that regard the analysis had shown that all of the AIIAs were able to treat to target but beyond that it had not investigated any additional BP lowering efficacy. Conversely Bakris *et al* and Vidt *et al*, forced titrations of candesartan and losartan (Cozaar), showed that candesartan was more effective than losartan in lowering BP when both were administered once daily at maximum doses. Bakris *et al* reported that candesartan lowered mean sitting trough BP by 13.3/10.9mmHg compared with a mean reduction of 9.8/8.7mmHg by losartan at week 8 – a difference of 3.5/2.2mmHg. The difference between the two products with regard to mean sitting trough BP as reported by Vidt *et al* was 3.3/1.4mmHg.

The Appeal Board noted that small differences in BP lowering, such as reported by Bakris *et al* and Vidt *et al* could be clinically meaningful. In that regard the Appeal Board noted that a table of results in the Cochrane analysis showed similar differences between some of the AIIAs albeit by indirect comparison.

The Appeal Board considered the claim 'A new independent Cochrane review suggests that "there were no clinically meaningful BP lowering differences between available [AIIAs]"' inferred that it had been proven that there were no clinically meaningful blood pressure lowering differences between available AIIAs which was not so especially in light of the evidence from Bakris *et al* and Vidt *et al* which directly compared candesartan and losartan. The Appeal Board considered that the claim did not reflect the totality of the available evidence and it was misleading. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3 of the Code. The appeal was unsuccessful.

Complaint received **6 March 2009**

Case completed **12 June 2009**