CASE AUTH/2085/1/08 and AUTH/2086/1/08

MEDIA/DIRECTOR V MERCK SHARP & DOHME AND SCHERING-PLOUGH

Ezetrol insert in The Pharmaceutical Journal

A letter published in The Pharmaceutical Journal from a pharmacist at a primary care trust entitled 'Many people do not take statins as described', criticised a four page promotional insert for Ezetrol (ezetimibe) jointly sponsored by Merck Sharp & Dohme and Schering-Plough. The insert was entitled 'NICE guidance on ezetimibe: A pharmacist's perspective' and was written by a pharmacist, from an NHS Trust. Prescribing information for Ezetrol was on the back page.

The complainant was particularly critical that the insert did not refer to patient compliance with statins. The complainant also alleged that five year old data was cited in support of the claim 'Thirty five percent of patients with coronary heart disease in the UK are not reaching current government cholesterol targets despite effective treatment therapies'. The claim, however, was not supported by the data; when patients had their statin therapy reviewed then only 22% failed to reach target (Brady *et al* 2005). The complainant further noted that Brady *et al* did not state that ezetimibe had no robust cardiovascular disease outcome data, in contrast to a number of statins; something to be considered when deciding how to treat a patient who had not reached target.

In accordance with established procedures the matter was taken up by the Director as a complaint under the Code.

The Panel noted that the insert at issue was a review of the NICE guidance on ezetimibe for the treatment of primary hypercholesterolaemia. In patients with primary hypercholesterolaemia, Ezetrol was indicated for use together with a statin where the statin alone had not appropriately controlled the patient's lipid levels (Ezetrol Summary of Product Characteristics (SPC)). Given the aim of the insert and Ezetrol's licensed indication, the Panel did not consider that it was misleading not to refer to patient compliance as a reason for the failure of statin monotherapy. No breach of the Code was ruled.

The claim 'Thirty five percent of patients with coronary heart disease in the UK are not reaching current government cholesterol targets despite effective treatment therapies' which was referenced to Brady *et al* published in 2005; the companies submitted that there had not been any more recent publications in the UK. Some of the data in Brady *et al* was from May 2000. The authors set out to see whether national cholesterol targets were being met ie that statin therapy should reduce serum total cholesterol to <5mmol/L or by 25% whichever resulted in the lowest achieved level. The data showed that success in lowering cholesterol to <5mmol/L was achieved with the first dose of statin in 65% of patients and in 78% following titration or switching. It thus appeared that the 35% of patients not reaching target levels and referred to in the claim were only those who had total cholesterol of <5mmol/L on the first dose and had yet to be titrated or switched. Such additional therapy or change of therapy reduced the figure of 35% to 22%. In addition the claim did not take account of the target of reducing total cholesterol by 25%. The Panel considered that the claim was too general given the additional data; it only applied in limited circumstances. In that regard the claim was misleading, exaggerated and could not be substantiated. Breaches of the Code were ruled.

The Panel did not consider that it was misleading not to state that Ezetrol had no robust cardiovascular disease outcome data, in contrast to a number of statins. In the Panel's view readers would know the importance of lowering cholesterol and the role of surrogate markers for cardiovascular disease and that if a statin failed to bring a patient to target other therapies such as Ezetrol should be added. Ezetrol was effective in lowering surrogate markers of cardiovascular disease ie total cholesterol and LDL-cholesterol. No breach of the Code was ruled.

A letter published in The Pharmaceutical Journal from a pharmacist, at a primary care trust, entitled 'Many people do not take statins as described', criticised a four page promotional insert for Ezetrol (ezetimibe) jointly sponsored by Merck Sharp & Dohme Limited and Schering-Plough Ltd. The insert had been distributed with The Pharmaceutical Journal. The insert was entitled 'NICE guidance on ezetimibe: A pharmacist's perspective' and was written by a pharmacist, from an NHS Trust. Prescribing information for Ezetrol was on the back page.

In accordance with established procedures the matter was taken up by the Director as a complaint under the Code. The author of the letter indicated that he wanted to be involved in the complaint process.

COMPLAINT

In his letter the complainant stated that it was important that a pharmacist took the utmost care when publicly supporting an advertisement in The Pharmaceutical Journal particularly when that pharmacist was employed by the NHS to give prescribing advice. The insert advertising ezetimibe

was a case in point. No mention was made of patient compliance. In primary care it was often the case that patients' cholesterol levels were not on target because they did not take their statin as prescribed. There were many reasons for poor compliance, and primary care pharmacists were in a good position to explore these and find solutions. Similarly, community pharmacists could help with judicious use of medicines use reviews. The complainant was disappointed that the author of the insert omitted this important issue in his article.

The complainant alleged that the insert used a five-year-old survey published in the British Journal of Cardiology to support a claim that 'Thirty-five percent of patients with coronary heart disease in the UK are not reaching current government cholesterol targets despite effective treatment therapies'. There was no mention in the survey of the statin doses used except to state that the figure improved to 22% after review of statin treatment. This hardly supported the claim.

The author also did not state that ezetimibe had no robust cardiovascular disease outcome data, in contrast to a number of statins. This should be considered when deciding which path to follow when a patient was not to target.

When writing to the companies, the Authority asked them to respond in relation to Clauses 7.2, 7.4 and 7.10.

RESPONSE

Merck Sharp & Dohme and Schering-Plough stated that the purpose of the insert in The Pharmaceutical Journal was to alert its readers to the recent NICE guidance about ezetimibe which was published on the NICE website in September 2007. The insert was structured as follows:

- Page 1 - provided an introductory overview of the whole NICE guidance from a pharmacist's perspective;
- Page 2 - gave a succinct, fair and balanced summary of the 31 page NICE guidance on ezetimibe so that the key conclusions with respect to its recommended use in the NHS in terms of clinical and cost-effectiveness were accurately portrayed in a readily assimilated form;
- Page 3 - depicted how this new guidance might be applied in routine clinical practice and in accordance with previous NICE guidance on statins by providing a hypothetical example of the treatment options available for suitable patients. The 40mg dose of simvastatin was chosen for the treatment algorithm as this was now the most widely prescribed dose;
- Page 4 - included the requisite prescribing information.

Patient compliance

a) Title of the letter

The companies noted that the title of the letter, 'Many people do not take statins as described', indicated the key issue that the author wished to draw the readers' attention was patient compliance (see also comments below). Whereas the NICE guidance for ezetimibe referred to statins, this was only in the context of its two main indications being either monotherapy, when patients were unable to tolerate statins or they were contraindicated, or as combination therapy when additional efficacy in cholesterol lowering was required.

The companies submitted that statins per se, were not the focus of the NICE guidance at issue; the guidance did not refer to statin compliance. The nature and purpose of the insert was made clear throughout. At the top of the first page in large, bold type and capital letters was the heading 'NICE GUIDANCE ON EZETIMIBE:' The second page of the insert similarly had the large heading 'NICE GUIDANCE – SUMMARY' clearly displayed. Consequently the reader was left in no doubt as to what the insert related, namely the guidance issued by NICE. The insert was not intended to provide a complete overview of all aspects of the management of patients with hypercholesterolaemia. Nonetheless, the author stated in the third paragraph what was current practice in the UK, until the introduction of this new guidance, as follows 'Current prescribing practice if a patient's cholesterol is not managed to government recommended targets of 5mmol/l for total cholesterol (TC) and 3mmol/l for a low density lipoprotein cholesterol (LDL-C) is to up-titrate a generic statin dose, or to switch to an alternative branded statin.'

b) No mention was made of patient compliance

The companies acknowledged that patient compliance could be a major issue for prescribed medicines and pharmacists would wish to ensure they were appropriately used so as to maximise the benefit they might provide and lessen the chances of unwanted side effects. However, the purpose of the insert was to summarise the NICE guidance on ezetimibe, which did not refer to patient compliance and statins. Hence it was not included.

c) No mention was made of the role of primary care pharmacists in exploring the reason for poor compliance (of statins) and finding solutions

The companies submitted that strategies to improve compliance of cholesterol lowering agents would be welcomed, however, this was not addressed in the NICE guidance for ezetimibe. These issues were, however, referred to in the second paragraph of the insert where the author stated 'The NICE guidance is of particular interest to pharmacists as it applies directly to our daily work in providing prescribing guidance on cholesterol management'. It was also referred to in paragraph 3, where he stated that pharmacists looked at a variety of factors before prescribing or providing guidance on lipid lowering management, including the efficacy, tolerability and cost of a treatment.

The companies submitted that whilst the appropriate

use of statins and patient compliance was undoubtedly an important feature in general practice, (and indeed a constant challenge for all medicines administered for chronic and largely asymptomatic medical conditions), it was neither referred to in the NICE guidance for ezetimibe nor in the Ezetrol summary of product characteristics (SPC). Consequently it was not referred to in the insert as it was something all pharmacists should take heed of in relation to all medicines.

The suggestion that the author, a pharmacist employed by the NHS to give prescribing advice, might not have taken utmost care when supporting the insert

The companies submitted that the author was chosen to provide his personal perspective on the NICE guidance. He had sufficient experience to comment on this issue as he was a prescribing consultant pharmacist to primary care and was currently involved in nurse prescribing and the British Heart Foundation at national level-qualifications, which indicated that he was intimately involved in this therapeutic area. His personal perspective represented his independent and sincerely held beliefs on the matter and the insert was reviewed by certified signatories, for compliance with the Code rather than challenging certain non-specific factors that pharmacists should take into account when advising patients on their medicines, such as patient compliance. Declarations and sponsorship were prominently declared.

The insert used a 5 year old survey published in the British Journal of Cardiology to support its claim that thirty-five percent of patients with coronary heart disease in the UK were not reaching targets despite effective treatments

Brady *et al* (2005) had been used to support this claim. The full reference for this publication was given on the last page of the insert. The complainant was therefore wrong to state that the survey was five years old. In addition it was a highly appropriate reference to use as it was drawn from the MediPlus database, run by IMS, involved 8,434 subjects and was published in a peer-reviewed journal by a consultant cardiologist.

The companies submitted that as the insert was prepared in December 2007, it was entirely in keeping to use a paper which was only 2 years old. Nonetheless, the companies had searched Medline search using 'statin prescribing in the UK' and 'achievement of cholesterol targets' to see if there had been any more recent publications in the UK and none were found. Thus Brady *et al* was the most up-to-date and current data in the public domain.

The claim that 35% of patients with coronary heart disease in the UK were not reaching current government targets despite effective treatment therapies was from Brady *et al* which showed that for all 8,434 subjects analysed in the survey only 5,516 (65.4%) achieved a target reduction of < 5mmol/l. The paper also displayed various different treatment scenarios with the accompanying target attainment. Rather than being selective in using these different sub groups, it was more representative to use the figure given for the whole database, as this was more likely to reflect current practice and thus the reality of statin prescribing in primary care. The complainant was therefore incorrect in assuming that the 35% related to target attainment when initiating statin therapy.

The use of such a population-based approach was in line with that taken by NICE, which considered target attainment in the patient population as a whole, and not certain sub segments. This was borne out by the NICE guidance for ezetimibe which stated that 'In England, the average total cholesterol concentration in adults is approximately 5.6 mmol/litre' (Brady *et al*). Clearly this indicated that for the population as a whole, 50% of people had cholesterol values > 5 mmol/l which would more than adequately support the assumption from the MediPlus database that 35% of patients with CHD had cholesterol values > 5 mmol/l.

There was no mention of the statin doses used except to say that the figure improved to 22% after review of statin treatment

The companies submitted that although Brady *et al* did not mention specific doses for the statins, it further sub divided the results according to whether patients were on their initial statin dose, titrated once, twice or more, titrated and switched, switched not titrated or any titration and switch, so there were plenty of ways that the data could be analysed according to the different management paths taken.

The achievement of the target attainment of <5 mmol/l for patients who had both a titration and switch was 78%. However this was only achieved in 1,478 subjects (17.5%) and so this neither reflected common practice nor the reality of statin prescribing in the UK.

The author of the insert also omitted to state that ezetimibe had no robust cardiovascular disease outcome data, in contrast to a number of statins. This should be taken into account when deciding which path to follow when a patient was not at target

The companies submitted that section 4.1.1 of the NICE guidance for ezetimibe briefly referred to the lack of any outcome studies but the appraisal committee dismissed this in terms of its assessment of clinical outcomes as follows; 'No studies reported health-related quality of life or clinical end points such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and TG concentrations were used as indicators of clinical outcomes'. Section 4.3.5 also stated that 'The Committee agreed that there is sufficient evidence to link reductions in LDL cholesterol concentrations induced by treatment with ezetimibe with future reductions in cardiovascular events'.

In a summary review of the NICE guidance for ezetimibe the companies submitted that it would be inappropriate to make comparisons with the statins which were outside the scope of the review.

Page 3 of the insert depicted a hypothetical treatment algorithm which reflected common UK practice, the NICE guidance for the use of statins and Section 4.3.11 of the NICE guidance for ezetimibe which stated that 'The Committee agreed that therefore adding ezetimibe to initial statin therapy as a treatment option is a cost effective use of NHS resources when compared with switching to an alternative statin'.

In conclusion the companies submitted that although the complainant made some valid points regarding patient compliance and the role that primary care pharmacists might be able to play, these issues should be debated among pharmacists. The insert accurately reflected the NICE guidance on ezetimibe and so was accurate, balanced, fair, objective, unambiguous, based on an up-to-date evaluation of all the evidence, substantiable and promoted the rationale use of medicines in line with NICE guidance. The companies therefore refuted the alleged breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

PANEL RULING

The Panel noted that the insert at issue was a review of the NICE guidance on ezetimibe (Ezetrol) for the treatment of primary hypercholesterolaemia. In patients with primary hypercholesterolaemia, Ezetrol was indicated for use together with a statin where the statin alone had not appropriately controlled the patient's lipid levels (Ezetrol SPC). Given the aim of the insert and Ezetrol's licensed indication, the Panel did not consider that it was misleading not to refer to patient compliance as a reason for the failure of statin monotherapy. No breach of Clause 7.2 was ruled.

The Panel noted that page 3 of the insert included the claim 'Thirty five percent of patients with coronary heart disease in the UK are not reaching current government cholesterol targets despite effective treatment therapies' which was referenced to Brady *et al*. Brady *et al* was published in 2005; the companies submitted that there had not been any more recent publications in the UK. Brady *et al* was in two parts. Firstly, Mediplus prescribing database of 80,000 patients with established CHD of which 8434 were on a statin, sampled from May 2000. This data was examined up until December 2002 before the availability of rosuvastatin or ezetimibe to see where cholesterol targets were met at that time and to determine prescribing patterns. Secondly, in January 2003 a postal survey of GPs who had contributed to the Mediplus database. The dual surveys were to show the difference between expectation and actual achievement in statin prescribing in the UK general practice. The authors set out to see whether national cholesterol targets were being met ie that statin therapy should reduce serum total cholesterol to <5mmol/L or by 25% whichever resulted in the lowest achieved level. The data showed that success in lowering cholesterol to <5mmol/L was achieved with the first dose of statin in 65% of patients and in 78% following titration or switching. It thus appeared that the 35% of patients not reaching target levels and referred to in the claim were only those who had total cholesterol of <5mmol/L on the first dose and had yet to be titrated or switched. Such additional therapy or change of therapy reduced the figure of 35% to 22%. In addition the claim did not take account of the target of reducing total cholesterol by 25%. The Panel considered that the claim was too general given the additional data; it only applied in limited circumstances. In that regard the claim was misleading, exaggerated and could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

The Panel did not consider that it was misleading not to state that Ezetrol had no robust cardiovascular disease outcome data, in contrast to a number of statins. In the Panel's view readers would know the importance of lowering cholesterol and the role of surrogate markers for cardiovascular disease and that if a statin failed to bring a patient to target other therapies such as Ezetrol should be added. Ezetrol was effective in lowering surrogate markers of cardiovascular disease ie total cholesterol and LDL-cholesterol. The Panel did not consider that the insert was misleading with regard to the failure to mention that Ezetrol had no cardiovascular disease outcome data. No breach of Clauses 7.2, 7.4 and 7.10 was ruled.

Proceedings commenced	**25 January 2008**
Cases completed	**10 March 2008**