CASE AUTH/1802/2/06

TEACHING PRIMARY CARE TRUST HEAD OF MEDICINES MANAGEMENT v MERCK

Glucophage SR journal advertisement

The head of medicines management at a primary care trust complained about a journal advertisement for Glucophage SR (prolonged release metformin) issued by Merck. The complainant alleged that the claim 'More GI-friendly than IR [immediate release] metformin!' could not be substantiated. No references were cited in support of the claim and the summary of product characteristics (SPC) clearly suggested that gastrointestinal (GI) symptoms were very common with Glucophage SR.

The complainant further stated that the writing in the advertisement was so small he had had to use a magnifying glass to read it.

The Panel noted that the advertisement seemed to have been written across someone's belly. The headline claim 'More GI-friendly than IR metformin!' appeared immediately above a cartoon style smiling face (the mouth of which seemed to be the belly button). The Panel considered that the advertisement implied that GI side effects were not too much of a problem with Glucophage SR. According to the SPC, however, such side-effects occurred very commonly (>1/10) with Glucophage SR as they did with Glucophage (metformin IR). The Panel noted the comparative data submitted but nonetheless considered that the claim, in the context in which it appeared, gave a misleading impression of the absolute incidence of GI effects seen with Glucophage SR which could not be substantiated. Breaches of the Code were ruled.

The Panel noted that the prescribing information at issue was in thin, white type printed on a flesh coloured background. The Panel considered that the poor contrast between the colour of the text and the background was such that the prescribing information was not easy to read. A breach of the Code was ruled.

The head of medicines management at a primary care trust complained about a journal advertisement (ref December 2005. zz27110) for Glucophage SR (prolonged release metformin) issued by Merck Pharmaceuticals which appeared in Prescriber on 19 February.

COMPLAINT

The complainant noted that no references were cited in support of the claim 'More GI-friendly than IR [immediate release] metformin!' except for the reader to obtain further information from the manufacturer. The complainant further noted that the SPC clearly suggested that GI symptoms were very common with Glucophage SR! If the reader wanted to substantiate the claims made by Merck there was nothing to refer to.

The complainant stated that in advertisements with such headline statements, readers should be given a reference to help make the decision for themselves.

The complainant alleged that Merck could not substantiate the claim that Glucophage SR was more 'GI-friendly than IR metformin!' and that it was trying to deceive clinicians.

The complainant further stated that the writing in the advertisement was so small he had had to use a magnifying glass to read it.

When writing to Merck, the Authority asked it to respond in relation to Clauses 4.1, 7.2 and 7.4 of the Code of Practice.

RESPONSE

Merck stated that the Glucophage SR advertisement was developed in a number of sizes such that the smallest version, ie the one at issue, complied with the Code and thus that a lower case 'x' in the prescribing information was at least 1mm in height. Merck's printer had confirmed compliance with regards sizing. Furthermore the prescribing information was clearly positioned alongside the advertisement with short well-spaced lines, emboldened headings and in a contrasting typeface. Merck therefore did not accept there had been a breach of Clause 4.1 of the Code.

Metformin, as an immediate release formulation (Glucophage), had been used for nearly 50 years to treat type 2 diabetes. GI disturbances were widely accepted as the principal adverse effects of treatment and occurred in about 20% of patients. Diarrhoea was the most frequent unwanted effect and although it tended to diminish with time it led to discontinuation of treatment in about 5% of patients (Howlett and Bailey, 1999).

A prolonged-release (SR) form of metformin had been available in the US since October 2000 and was launched in the UK as Glucophage SR in January 2005. In double-blind placebo controlled trials diarrhoea led to discontinuation of Glucophage in 6% of patients. By contrast, as stated in the Physicians' Desk Reference, in placebo-controlled trials with Glucophage SR only 0.6% discontinued due to diarrhoea.

In a double-blind direct comparison of twice daily IR metformin with once daily SR metformin, in those receiving the same total daily dose, the incidence of treatment-emergent GI events was 39% and 29% respectively (Fujioka *et al*, 2003).

A study assessing patients' treatment records from routine clinical care in the US evaluated GI tolerability and incidence of diarrhoea with SR metformin compared with IR metformin. In a group of 205 patients that were switched from IR metformin to SR metformin there was a 50% reduction in the first year of therapy in the frequency of any GI adverse events (26.34% IR, 11.71% SR, $p<0.001$) with a similar

reduction for diarrhoea (18.05% IR, 8.29% SR, p<0.01) (Blonde *et al*, 2004). The switch was also associated with significantly improved GI tolerability in a subgroup of 78 patients that switched from IR metformin to SR metformin with the intention of relieving GI symptoms (p<0.01) (Davidson and Howlett, 2004). When comparing those patients that received metformin for the first time, there was a significantly lower incidence of GI side effects in the first year of treatment on SR metformin (9.23%) than IR metformin (19.83%) (p<0.05). Again the findings were similar for the incidence of diarrhoea (3.08% SR, 13.50% IR, p<0.05) (Blonde *et al*).

The Glucophage SR SPC stated that the nature and severity of adverse events were similar to those reported with immediate release metformin. It was notable that there was no comparative statement with regard to frequency. For frequency of adverse events the SPC only used the crude classification of very common, common etc. Merck acknowledged that the incidence of GI effects with Glucophage SR using this classification was very common ie greater than 1 in 10 patients. However, the evidence cited above demonstrated that although still very common the incidence of GI events with Glucophage SR was lower than that reported with IR metformin.

Therefore the claim that Glucophage SR was 'More GI-friendly than IR metformin!' was accurate, up-to-date, not misleading and capable of substantiation. Merck did not accept there had been a breach of Clauses 7.2 or 7.4 of the Code.

Furthermore, if the complainant had asked Merck for information to support the claim, the references cited above would have readily been supplied in compliance with Clause 7.5 of the Code.

PANEL RULING

The Panel noted that the advertisement seemed to have been written across someone's belly. The headline claim 'More GI-friendly than IR metformin!' appeared immediately above a cartoon style smiling face (the mouth of which seemed to be the belly button). The Panel considered that the advertisement implied that GI side effects were not too much of a problem with Glucophage SR. According to the SPC, however, such side-effects occurred very commonly (>1/10) with Glucophage SR as they did with Glucophage (metformin IR). The Panel noted the comparative data submitted but nonetheless considered that the claim, in the context in which it appeared, gave a misleading impression of the absolute incidence of GI effects seen with Glucophage SR which could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that Clause 4.1 required prescribing information to be provided in a clear and legible manner. The supplementary information made a number of recommendations to aid legibility; type size was not the only contributory factor. The prescribing information at issue was in thin, white type printed on a flesh coloured background. The Panel considered that the poor contrast between the colour of the text and the background was such that the prescribing information was not easy to read. A breach of Clause 4.1 was ruled.

Complaint received	**23 February 2006**
Case completed	**31 March 2006**