CASE AUTH/2338/7/10

ESPRIT v DEXCEL PHARMA

Deximune mailing

ESPRIT (Efficacy and Safety of Prescribing in Transplantation) alleged that a one page, A4 mailing for Deximune (ciclosporin) sent by Dexcel Pharma, headed 'Ciclosporin Prescribing in the UK The Facts', had the potential to negatively impact patient safety.

ESPRIT noted that official UK recommendations clearly stated if it was necessary to switch a patient stabilised on one brand of ciclosporin to another brand, the patient should be monitored closely for side-effects, blood-ciclosporin concentration and transplant function.

ESPRIT supported these recommendations which were in line with its own recommendations. Unfortunately the mailing at issue, particularly the assertion that patients could be switched without the need for dose adjustment, with no stipulation for monitoring, was at odds with such recommendations, which were made in the interest of patient safety. Indeed, ESPRIT believed it was contrary to the provisions of the Deximune summary of product characteristics (SPC).

The detailed response from Dexcel Pharma is given below.

The Panel noted that the mailing at issue featured a number of claims in bold, bright blue font. One of these was 'There is no significant difference between the absorption of ciclosporin from Deximune and Neoral under fed and fasted conditions'. This was immediately followed, in plain, black type by the next paragraph which began 'Because of the differences in absorption between fed and fasted conditions with previous formulations of ciclosporin the current recommendations are for close monitoring when switching any formulation of ciclosporin.' This was, in turn, followed by another claim in bold, bright blue font that 'However, patients can be started on Deximune or switched to Deximune from Neoral without the need for dose adjustment'.

The Deximune SPC stated the following:

'Due to differences in bioavailability between different oral formulations of ciclosporin it is important that health professionals and patients be aware that substitution of Deximune Capsules for other formulations may lead to alterations in ciclosporin blood levels.

Therefore patients should not be transferred to or from other oral formulations of ciclosporin without appropriate close monitoring of ciclosporin blood concentrations, serum creatinine levels and blood pressure.'

The Panel noted the presentation and layout of the mailing and considered that the reader's eye would be drawn to the claims in bright blue text such that they were likely to overlook the statement inbetween about the current recommendations for close monitoring. In the Panel's view, however, the statement regarding monitoring was, in any case, insufficient in that the Deximune SPC specifically referred to the close monitoring of ciclosporin blood concentrations, serum creatinine levels and blood pressure. The Panel noted that although the mailing had been used with hospital consultants, it had also been used widely with non-specialist health professionals. In the Panel's view, although some of the target audience would be experienced and knowledgeable about the use of ciclosporins, and thus familiar with content of the SPCs with regard to switching, others would not and so detailed knowledge in that regard should not be assumed. Overall, the Panel considered that the mailing was misleading with regard to the precautions necessary when switching a patient from Neoral to Deximune. A breach of the Code was ruled. The Panel considered that the claims were not consistent with the particulars listed in the Deximune SPC. A breach of the Code was ruled.

The Panel noted its comments above and considered that the mailing had the potential to adversely affect patient safety. Although there were no reports before the Panel to suggest that patient care had been adversely affected, it nonetheless considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel did not consider that the matter was such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 of the Code was ruled.

ESPRIT (Efficacy and Safety of Prescribing in Transplantation) complained about a one page, A4 mailing for Deximune (ciclosporin) sent by Dexcel Pharma Limited. The mailing was headed 'Ciclosporin Prescribing in the UK The Facts'.

COMPLAINT

ESPRIT was concerned that the mailing at issue had a real potential to negatively impact patient safety and in that regard noted that official recommendations regarding use of different formulations of ciclosporin were clear, as exemplified by the following:

> 'Patients should be stabilised on a single brand of oral ciclosporin because switching between

formulations without close monitoring may lead to clinically important changes in bioavailability. Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching. If it is necessary to switch a patient stabilised on one brand of ciclosporin to another brand, the patient should be monitored closely for side-effects, blood-ciclosporin concentration, and transplant function.' (ref current British National Formulary (BNF)).

and

'Patients should be stabilised on a single brand of ciclosporin because switching between formulations without monitoring may lead to clinically important changes in bioavailability. All products that contain ciclosporin are interchangeable **only** if careful therapeutic monitoring takes place. Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching.' (ref Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Update, December 2009)

ESPRIT fully supported these recommendations. Indeed, they were wholly in line with its own recommendations made following an in-depth examination of available data. Unfortunately, the mailing at issue, particularly the assertion that patients could be switched without the need for dose adjustment, with no stipulation for monitoring, was at odds with such recommendations, which were made in the interest of patient safety. Indeed, ESPRIT believed it was contrary to the provisions of the Deximune summary of product characteristics (SPC).

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

RESPONSE

Dexcel submitted that Deximune had been demonstrated to be bioequivalent to Neoral. This was confirmed by healthy volunteer studies under fed and fasting conditions. The data from these studies was included in the Deximune SPC. In addition, a post-marketing, retrospective, parallel, multicenter survey in transplant patients receiving these two formulations compared their toxicity profiles and bioavailability (Berger *et al* 2008). Of the patients reviewed, 157 out of 174 received both products; Neoral was administered first and then the patients were transferred to Deximune. Ciclosporin blood levels measurements were taken on three occasions during the review period. The results confirmed the bioequivalence of the two products in this patient population using analytical programs which took account of the patient variables. In addition, the products were deemed to have similar toxicity profiles and as a result the investigators concluded that the two products could be interchanged without the need for dosage adjustment while monitoring blood levels, blood pressure and renal function, all of which were recorded in the study.

UK patients were last switched from one formulation of ciclosporin to another when Neoral was introduced; over a period of time the majority of patients were switched from Sandimmune to Neoral. Dexcel understood from prescribers that patients were switched on a dose for dose basis which resulted in changes in trough ciclosporin levels and rejection episodes for a number of patients. As a result, a significant number of prescribers had been concerned about the appropriate dose to start patients on Deximune, either *de-novo* or when switching from Neoral.

In the light of the bioequivalence information outlined above and the concern about the appropriate starting and switching dose for Deximune, this was an important issue that needed to be addressed. It was important from a safety point of view therefore to highlight the fact that when starting new patients on Deximune or when transferring patients from Neoral to Deximune, the dose should be the same as for Neoral. For this reason, the claim 'However patients can be started on Deximune or switched to Deximune from Neoral without the need for dose adjustment' was highlighted in the mailing to minimise the risk that a patient might be transferred on a higher or lower dose and so potentially be at risk of rejection or toxicity.

ESPRIT had claimed that Dexcel made no stipulation for monitoring, which was not so; the mailing clearly stated 'Because of the differences in absorption between fed and fasted patients with previous formulations of ciclosporin, the current recommendations are for close monitoring when switching any formulation of ciclosporin'. This claim immediately preceded the one regarding the starting dose which Dexcel considered was the appropriate positioning from a patient safety point of view. Dexcel had never, either verbally or in writing, suggested that Neoral patients should be switched to Deximune without close monitoring to confirm ciclosporin blood levels, renal function and blood pressure.

In December 2009 at the request of the MHRA, Dexcel sent a 'Dear Healthcare Professional' letter to 54,364 health professionals including: GPs; retail and hospital pharmacists; hospital doctors (from staff grade to professor) within dermatology, nephrology, paediatric nephrology, renal, rheumatology and transplant and pharmaceutical advisors in primary care trusts. This letter was approved by the MHRA and could be viewed on its website. The letter clearly highlighted the need to prescribe ciclosporin by brand, for close monitoring to be carried out when switching and that transplant patients should not have their brand of ciclosporin changed without the permission of the prescriber. This was the only communication that Dexcel had had with the majority of these health professionals.

By contrast, the mailing at issue was sent only to hospital consultants in renal medicine, transplantation and dermatology; hospital pharmacists; pharmaceutical advisors and medicines management pharmacists within primary care trusts; a total of 3,890 health professionals. The mailing had also been used subsequently at the British Renal Association/Renal Society joint meeting in May, The British Association of Dermatology meeting in July and in discussions with professionals who fell within the above groups. It would be reasonable to assume that these professionals were well informed on the need for close monitoring when prescribing ciclosporin for patients, particularly when switching between brands. However, as noted above, Dexcel considered it appropriate to remind them of the need for close monitoring when switching between brands. In addition, at no time after the mailing was sent or in subsequent 1:1 conversations, had any health professional complained to Dexcel about the content of the mailing. Furthermore, in the 10 months that Deximune had been available in the UK, Dexcel had had no reports of an adverse reaction as a result of a patient being switched from Neoral to Deximune.

Dexcel understood ESPRIT's concerns about ciclosporin prescribing. The group had worked closely with another pharmaceutical company over the last ten years to develop a consensus statement on ciclosporin based on experience of a number of generic formulations of ciclosporin that had been available in countries other than the UK. Their conclusions had shaped the current UK guidelines and recommendations.

Dexcel acknowledged that ESPRIT was now an independent organisation, and it had been keen to support its activities. In doing so Dexcel intended to ensure that it promoted Deximune in a responsible way and where appropriate, provided support to prescribers and patients when the ciclosporin of choice was Deximune. Notwithstanding that, Dexcel also needed to provide prescribers and potential prescribers with appropriate information for them to make an informed choice about which ciclosporin product to use. Decisions about ciclosporin prescribing were in the main made by hospital consultants, hospital pharmacists, primary care medicines management pharmacists and senior managers at hospital and PCT level. As a result, Dexcel's promotional activity had been mainly directed at these individuals.

In Dexcel's promotion of Deximune it had looked to convince the decision makers to arrive at an informed choice based on the clinical evidence and the cost effectiveness for Deximune. Dexcel had always taken into account patient safety and had never promoted Deximune outside of the scope of the SPC.

Dexcel submitted that it always aimed to work to the highest standards when producing its promotional materials and believed that the mailing at issue was no exception. Whilst highlighting the appropriate dose at which Deximune should be started for either new or switch patients, Dexcel had also included the current recommendations about close monitoring. In addition, in view of the fact that Dexcel had communicated with a well informed audience this further strengthened the point that patients had not been put at risk. Dexcel denied any breach of the Code.

PANEL RULING

The Panel noted that the mailing at issue featured a number of claims in bold, bright blue font. One of these was 'There is no significant difference between the absorption of ciclosporin from Deximune and Neoral under fed and fasted conditions'. This was immediately followed, in plain, black type by the next paragraph which began 'Because of the differences in absorption between fed and fasted conditions with previous formulations of ciclosporin the current recommendations are for close monitoring when switching any formulation of ciclosporin.' This was, in turn, followed by another claim in bold, bright blue font that 'However, patients can be started on Deximune or switched to Deximune from Neoral without the need for dose adjustment'.

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misleading with regard to the precautions necessary when switching a patient from Neoral to Deximune. A breach of Clause 7.2 was ruled. The Panel considered that the claims were not consistent with the particulars listed in the Deximune SPC. A breach of Clause 3.2 was ruled.

The Panel noted its comments above and considered that the mailing had the potential to adversely affect patient safety. Although there were no reports before the Panel to suggest that patient care had been adversely affected, it nonetheless considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel did not consider that the matter was such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Complaint received **28 July 2010**

Case completed **10 September 2010**