CASE AUTH/2340/7/10

NOVARTIS v DEXCEL PHARMA

Promotion of Deximune

Novartis complained that a mailing and a detail aid for Deximune (ciclosporin), issued by Dexcel Pharma, failed to alert readers to the close monitoring that was required if patients stabilised on one brand of ciclosporin had to be switched to another. Novartis supplied Neoral (ciclosporin).

The detailed response from Dexcel Pharma is given below.

Novartis noted that recently updated UK guidance with regard to the switching of ciclosporin stated if it was necessary to switch a patient stabilised on one brand of ciclosporin to another brand, the patient should be closely monitored for side-effects, blood-ciclosporin concentration, and transplant function. Further, both the Deximune and Neoral summaries of product characteristics (SPCs) stated that patients should not be transferred to or from other oral formulations of ciclosporin without appropriate close monitoring of ciclosporin blood concentrations, serum creatinine and blood pressure.

Novartis noted that the mailing, 'Ciclosporin Prescribing in the UK The Facts', was available at the Dexcel stand at the British Transplant Society Annual Conference in March and was sent to the wider transplantation community including pharmacists. The claim at issue read 'Because of 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. *However, patients can be started on Deximune from Neoral without the need for dose adjustment.'* Noting the statement above from the Deximune SPC, Novartis submitted that use of the word 'however' and visual emphasis to the last sentence of the claim gave greater weight to the claim that no dose adjustment was required. Although this claim was true the visual emphasis to the final sentence allowed for ambiguity regarding the licensed requirement for close clinical monitoring of ciclosporin blood concentrations, serum creatinine levels and blood pressure, as stated in the Deximune SPC. Novartis alleged that this promotion was outside the terms of the marketing authorization.

Additionally, Novartis considered dose adjustments were a derivative of blood level monitoring and blood level monitoring to be a requirement of the terms of the marketing authorization. To claim that no dose adjustments were required when switching and visually emphasising this claim, created the perception that close blood level monitoring was not necessary or less important and thus misled the reader by implication and put the patient at risk of an inadvertent switch. Novartis noted that failure to closely monitor patients could lead to potential toxicity or underdosing with serious clinical implications including graft loss or death.

The Panel noted that in a closely similar complaint, Case AUTH/2338/7/10, it had 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 the 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 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 considered that its comments and rulings above in Case AUTH/2338/7/10 applied here in Case AUTH/2340/7/10. Breaches of the Code were ruled.

Novartis noted the claim on page 5 of the detail aid

that Deximune had been proved to: 'Be interchangeable with Neoral without the need for dose adjustment'. Nowhere in the detail aid were readers advised about the close monitoring of ciclosporin levels, serum creatinine and blood pressure which was required when switching between different formulations of ciclosporin.

Novartis submitted that claiming that no dose adjustments were required when switching, and by not providing any additional text to inform the reader of the need for close monitoring misled the reader and implied that close monitoring when switching patients was not necessary; this put the patient at risk of serious clinical implications. Novartis felt very strongly that the claims were inconsistent with the marketing authorization either by omission or through undue emphasis and implication.

The Panel noted that page 5 of the detail aid featured a number of bullet points about Deximune one of which stated that it had been proven to: 'Be interchangeable with Neoral without the need for dose adjustment'. The preceding bullet point stated that it had been proven to: 'Be equivalent to the innovator product, Neoral, under fed and fasted conditions'. There was no statement anywhere in the detail aid that if patients were switched from one brand of ciclosporin to another, close monitoring of ciclosporin blood concentrations, serum creatinine and blood pressure were required.

The Panel noted that the detail aid was available on-line for access by health professionals only. The Panel considered that a very wide audience might access the detail aid including those with little or no detailed knowledge of ciclosporin use. The Panel considered that the detail aid was misleading in its omission of detailed information about switching and not consistent with the Deximune SPC. Breaches of the Code were ruled. The Panel noted that Dexcel had not contested the complaint.

Novartis Pharmaceuticals UK Ltd complained about the promotion of Deximune (ciclosporin) by Dexcel Pharma Limited. At issue were a mailing (ref DEX/10/0013) and a detail aid (ref DEX/10/0001). Novartis supplied Neoral (ciclosporin). Inter-company dialogue had failed to resolve the matter.

By way of background Novartis noted that the recently updated guidance in the British National Formulary (BNF) with regard to the switching of ciclosporin stated:

> '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 closely monitored for side-effects, blood-ciclosporin concentration, and transplant function.'

Similarly, the December 2009 edition of the Drug Safety Update from the Medicines and Healthcare products Regulatory Agency (MHRA) stated:

> 'All products that contain ciclosporin should be prescribed by brand name to minimise the risk of inadvertent switching between brands, and to reflect advice in the British National Formulary.'

Novartis submitted that both the Deximune and Neoral summaries of product characteristics (SPCs) stated:

> '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/Neoral] 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 and blood pressure.'

A failure to remind of this requirement to carry out appropriate close monitoring was the basis of Novartis' complaint.

Novartis considered the materials at issue were not only in breach of the Code but also put patients at risk of harm; this was not a responsible way to promote a medicine in a complex therapeutic area. The potential cost of patient harm as a result of an uncontrolled inadvertent switch could be very high. Ciclosporin was routinely used not only in kidney but also heart and liver transplant, and in these patients acute rejection or toxicity could be fatal.

1 Mailing 'Ciclosporin Prescribing in the UK The Facts' (ref DEX/10/0013)

This mailing was available at the Dexcel stand at the British Transplant Society Annual Conference in March and, Novartis also believed, was sent to the wider transplantation community including pharmacists. The claim at issue read:

'Because of 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. **However, patients can be started on Deximune from Neoral without the need for dose adjustment.'**

COMPLAINT

Novartis noted the statement from the Deximune SPC above. The Code required any claim to be in accordance with the terms of the marketing authorization and to be accurate, objective, unambiguous and not to mislead either directly or

by implication or by undue emphasis.

Novartis submitted that use of the word 'however' and an emboldened typeface gave greater weight to the claim that no dose adjustment was required. Although this claim was true the bold type and implied extra weight to the final sentence allowed for ambiguity regarding the licensed requirement for close clinical monitoring of ciclosporin blood concentrations, serum creatinine levels and blood pressure, as stated in Section 4.2 of the Deximune SPC. Novartis considered that by allowing ambiguity in the interpretation of this paragraph through the bold text of the last sentence, the reader would question the requirement for therapeutic drug monitoring. Novartis alleged a breach of Clause 3.2 as the promotion was outside the terms of the marketing authorization.

Additionally, Novartis considered dose adjustments were a derivative of blood level monitoring and blood level monitoring to be a requirement of the terms of the marketing authorization. To claim that no dose adjustments were required when switching and emphasising this claim in bold text in a bright colour, created the perception that close blood level monitoring was not necessary or less important and thus misled the reader by implication and put the patient at risk of an inadvertent switch.

Novartis alleged that this indirect misleading of the reader by implication was in breach of Clause 7.2.

Novartis noted that failing to carry out appropriate close monitoring of patients could lead to potential toxicity or underdosing with serious clinical implications including graft loss or death. If readers were misled into thinking that dose for dose switching was advocated and that close monitoring was not important, it was not unreasonable to infer that some practitioners might be less rigorous with the necessary close monitoring, especially those not directly involved in the daily care of transplantation patients, like community pharmacists and thereby putting patients at risk of serious clinical implications, particularly in the community.

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, multicentre survey in transplant patients receiving these two formulations had compared their toxicity profiles and bioavailability (Berger *et al* 2008). Of the patients reviewed, 157 out of the 174 included received both products; Neoral was administered first and then the patients were transferred to Deximune. Ciclosporin blood level 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.

Deximune was currently the only alternative brand of ciclosporin available in the UK. Therefore the only switching that was likely to occur between oral formulations of ciclosporin was between Neoral and Deximune. 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 and due to lack of bioequivalence, this 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 prescribers' 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 text 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.

Dexcel noted Novartis' allegation that it had not been made it clear to the reader that patients switched from Deximune to Neoral should be closely monitored for a period following the switch. Dexcel noted that it was clearly stated in the mailing that '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 statement 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 professors) 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 letter 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 was 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 this 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 appreciated that Novartis would be concerned about an alternative brand of ciclosporin being available in the UK. Dexcel aimed to promote Deximune in a responsible manner and in doing so it hoped to provide prescribers with the appropriate information for them to make an informed choice on how and when to choose Deximune. 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 make an informed choice based on the clinical evidence and the cost effectiveness for Deximune. Dexcel had always taken patient safety into account and it had never promoted Deximune outside of the scope of the SPC. Dexcel did not believe that the mailing at issue was in breach of Clauses 3.2 or 7.2 and trusted that having considered Dexcel's response the Authority would agree.

PANEL RULING

The Panel noted that it had considered a closely similar complaint in Case AUTH/2338/7/10. The complaint in Case AUTH/2340/7/10 had been received before Case AUTH/2338/7/10 had been completed and so Case AUTH/2340/7/10 was allowed to proceed. The Panel referred to its ruling in Case AUTH/2338/7/10 with regard to the alleged breaches of Clauses 3.2 and 7.2.

Case AUTH/2338/7/10

The Panel noted that the mailing at issue (DEX/10/0013) 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 the 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 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.

Case AUTH/2340/7/10

The Panel considered that its comments and rulings above applied. Breaches of Clauses 3.2 and 7.2 were ruled.

2 Deximune detail aid (ref DEX/10/0001)

This detail aid was available on-line from www.deximune.co.uk.

COMPLAINT

Novartis noted that on page 5 of the detail aid there was a claim that Deximune had been proved to: 'Be interchangeable with Neoral without the need for dose adjustment'. This was not followed or preceded by any warning about the associated close monitoring required. There was also no mention of the licensed requirement of concurrent serum creatinine and blood pressure monitoring.

The marketing authorization of Deximune clearly stated:

> '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 and blood pressure.'

There was no mention anywhere in the detail aid of the close monitoring required by the terms of the marketing authorization when switching patients between formulations of ciclosporin.

The Code required the promotion of a medicine to be in accordance with the terms of its marketing authorization and consistent with the particulars listed in the SPC.

Novartis alleged that the lack of inclusion of text warning readers to perform the close monitoring of ciclosporin levels, serum creatinine and blood pressure when switching between different formulations of ciclosporin was in breach of Clause 3.2.

Novartis also believed the Code required claims to be accurate, objective and unambiguous and not to mislead either directly or by implication or by undue emphasis. Additionally, the material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine.

Novartis considered dose adjustments to be a derivative of blood level monitoring and blood level monitoring to be a requirement of the terms of the marketing authorization. Claiming that no dose adjustments were required when switching created the perception that close blood level monitoring was not necessary or less important, and by not providing any additional text to inform the reader of the need for close monitoring this was incomplete and misled the reader and implied that close monitoring when switching patients was not necessary, putting the patient at risk of serious clinical implications.

Novartis alleged that the omission of a statement about close monitoring as well as the indirect misleading of the reader through implication and by not providing any warning about close monitoring when switching, was in breach of Clause 7.2.

The serious clinical implications were highlighted by the MHRA Drug Safety Update 2009. Novartis considered that statements regarding interchangeability between formulations should always be accompanied by a statement about the requirement for close monitoring.

Novartis considered very strongly that the claims above did not adhere to the terms of the marketing authorization either by omission or through undue emphasis and implication, in breach of Clause 3.2.

Novartis also believed that the 'no need for dose adjustment' claim was highly likely to be misinterpreted; some prescribers would be misled into thinking that close monitoring was not important or required during switches, thereby breaching Clause 7.2.

RESPONSE

Dexcel noted that the detail aid was produced in September 2009 when it launched Deximune and reprinted in February 2010 as a result of a price change, without any further changes. The original brochure was one of a number of items which the MHRA viewed as part of the launch activities. At the time the MHRA was satisfied with the detail aid, which included the wording on page five that Novartis had highlighted. The MHRA did not require pre-vetting of any further promotional items.

However, in the light of this complaint and experience with Deximune to date, Dexcel had considered that this item would be improved by the inclusion of information about the need for close monitoring when switching patients from Neoral to Deximune. Dexcel therefore did not contest the complaint and would not circulate or distribute any more copies with immediate effect.

PANEL RULING

The Panel noted that page 5 of the detail aid featured a number of bullet points about Deximune one of which stated that it had been proven to: 'Be interchangeable with Neoral without the need for dose adjustment'. The preceding bullet point stated that it had been proven to: 'Be equivalent to the innovator product, Neoral, under fed and fasted conditions'. There was no statement anywhere in the detail aid that if patients were switched from one brand of ciclosporin to another, close monitoring of ciclosporin blood concentrations, serum creatinine and blood pressure were required.

The Panel noted that the detail aid was available on-line for access by health professionals only. The Panel considered that a very wide audience might access the detail aid including those with little or no detailed knowledge of ciclosporin use. The Panel considered that the detail aid was misleading in its omission of detailed information about switching. A breach of Clause 7.2 was ruled. The Panel considered that the detail aid was not consistent with the particulars listed in the Deximune SPC. A breach of Clause 3.2 was ruled. The Panel noted that Dexcel had not contested the complaint about the detail aid.

Complaint received **29 July 2010**

Case completed **3 September 2010**