PRIMARY CARE TRUST PRESCRIBING ADVISOR v FLYNN PHARMA

Distaclor MR email

The prescribing advisor to a teaching primary care trust (PCT) complained about an advertisement, emailed to GPs by Flynn Pharma, which promoted the prescribing of Distaclor (cefaclor) for patients following influenza as they might be susceptible to secondary bacterial respiratory tract infections. The email offered recipients starter packs of Distaclor. Cefaclor was a second-generation, broad-spectrum cephalosporin.

Distaclor MR was indicated in the treatment of a number of listed infections when caused by susceptible strains of the given organism. The summary of product characteristics (SPC) stated that studies to identify the causative organism and its susceptibility to cefaclor should be performed. Therapy might be started pending the outcome of the studies and adjusted when the results became available.

The complainant submitted that the use of broad-spectrum antibiotics was highly likely to increase the risk of resistance to antibiotics, and also led to the emergence of infections such as *Clostridium difficile*. In that regard the Health Protection Agency (HPA) had stressed that narrow-spectrum agents should be used for empirical treatment where appropriate and that the use of clindamycin and second and third-generation cephalosporins should be avoided, especially in the elderly.

The complainant stated that the local prescribing team endorsed the HPA guidance and that of local experts and considered that the advertisement, which offered free samples, went against that guidance and was surely inappropriate.

The detailed response from Flynn Pharma is given below.

The Panel noted that Flynn had offered starter packs not samples. The Code defined starter packs as a small pack designed to provide sufficient medicine for a primary care prescriber to initiate treatment when there might be an unavoidable delay in having a prescription dispensed. Antibiotics were appropriate to be given in starter packs.

The Panel considered that the mailing was confusing in that the content of the starter pack was not made clear; the starter pack offer was repeated immediately after reference to the calendar packs of 14 tablets. Flynn had submitted that the starter packs contained two tablets. Starter packs were not samples and thus not subject to the requirements of the Code which regulated the supply of samples. No breach of the Code was ruled in that regard.

The Panel noted that the advertisement stated that influenza might leave patients susceptible to secondary bacterial respiratory tract infections. Such patients might appreciate a free starter pack if seen out of hours or when the local pharmacy was closed. This was followed by two questions 'Do you have the time or the resources to find out which organism is responsible for your patients' secondary respiratory infections?' and 'Or do you need to prescribe a broad spectrum antibiotic which covers the most common bacterial causes?' followed by 'If so, consider Distaclor'.

The Panel noted that the complainant's PCT prescribing team discouraged the use of second- and third-generation cephalosporins in primary care as advised by the HPA and local experts. The Panel noted, however, that provided a medicine was promoted in such a way that was not inconsistent with its SPC, it was not necessarily unacceptable under the Code if that promotion was not in line with local or national guidelines.

In this instance the Panel considered that although the HPA advised against the use of, *inter alia*, second-generation cephalosporins, the advertisement at issue was not inappropriate as alleged. No breach of the Code was ruled.

Given its rulings above the Panel did not consider that high standards had not been maintained.

A prescribing advisor to a teaching primary care trust (PCT) complained about an advertisement for Distaclor (cefaclor) emailed by Flynn Pharma Ltd. Cefaclor was a second-generation, broad-spectrum cephalosporin.

The email in question had the subject header 'Flu season, free antibiotic starter packs'. The heading to the advertisement was 'Give your patients a head start with Distaclor MR starter packs'.

Distaclor MR was indicated in the treatment of a number of listed infections when caused by susceptible strains of the given organism. The summary of product characteristics (SPC) stated that studies to identify the causative organism and its susceptibility to cefaclor should be performed. Therapy might be started pending the outcome of the studies and adjusted when the results became available.

COMPLAINT

The complainant noted that the advertisement, emailed to GPs, promoted the prescribing of cefaclor for patients following influenza, as they might be susceptible to secondary bacterial respiratory tract infections.

The advertisement stated: 'Do you have the time or resources to find out what organism is responsible for your patients' secondary respiratory infections?'. It then offered free antibiotic starter packs, 14 days of cefaclor.

The complainant submitted that unnecessary use of broad-spectrum antibiotics was highly likely to increase the risk of resistance to antibiotics, and also led to the emergence of infections such as Clostridium difficile. In that regard the Health Protection Agency (HPA) stated in its guidance 'Clostridium difficile infection: How to deal with the problem' that restrictive antibiotic guidelines should be developed by trusts with the following recommendations stressed:

- Use narrow-spectrum agents for empirical treatment where appropriate.
- Avoid use of clindamycin and second- and third-generation cephalosporins, especially in the elderly.

The complainant's PCT prescribing team was dedicated and committed to advising prescribers on the appropriate use of antibiotics to ensure that they were used only when absolutely necessary. It strongly discouraged the prescribing of second- and third-generation cephalosporins in primary care, as advised by the HPA and local microbiologists, in an attempt to prevent the emergence of C.difficile. The advertisement at issue, which promoted the use of a broad-spectrum antibiotic and offered free samples, went against the HPA's advice and was surely inappropriate.

When writing to Flynn Pharma, the Authority asked it to respond in relation to Clauses 7.10, 9.1, 17.1 and 17.12 of the Code.

RESPONSE

Flynn stated that it knew that the incidence of C.*difficile* infections caused concern and naturally it supported activities which would lead to a reduction in the number of cases of this debilitating, and sometimes fatal, infection.

Flynn did not accept that the advertisement was in breach of the Code. In relation to the alleged breach of Clause 17 (provision of medicines and samples), the advertisement clearly offered 'starter packs' as distinct from 'samples' in this case two doses of treatment sufficient for a primary care prescriber to initiate treatment where there might be some undesirable or unavoidable delay'. The mailing specifically stated that the value of the starter packs was in the 'out of hours' situation and/or when 'the local pharmacy is closed'. This was in reality a question of good practice the benefits of which were generally recognised. Flynn appreciated however that the mailing did not specify the content of the starter pack as being two tablets and this would be amended in any subsequent communication.

Clause 7.10 required that promotion encouraged the rational use of a medicine. With regard to the specific complaint, the test was whether Flynn had inappropriately sought to encourage the use of a broad-spectrum antibiotic. The context of the mailing made clear in bold print statements that Distaclor might be considered where the prescriber did not have 'the time or resources to find out which organism is responsible' (for the secondary respiratory infection). Secondly it then specifically asked the prescriber to consider, 'do you need to prescribe a broad spectrum antibiotic…? 'and 'If so, consider Distaclor'. Flynn respectfully submitted that this was neither inappropriate or irrational. Broad-spectrum antibiotics were an important prescribing option in circumstances described and in particular, in primary care. The HPA and prescribing advisors were rightly concerned about indiscriminate and injudicious use. Flynn agreed with this position and need and hence the careful positioning and conditions for prescribing Distaclor were set out in the mailing.

Finally in regard to any alleged breach of Clause 9.1 (high standards), Flynn did not see that there was any case to answer.

Flynn submitted that it was an incontrovertible fact that influenza could lead to secondary bacterial respiratory tract infections through local damage to the respiratory tract epithelium and/or the development of a compromised immune function.

Faced with a patient recovering from influenza who presented with symptoms of a secondary bacterial upper respiratory tract infection (URTI) or lower respiratory tract infection (LRTI) a GP had three basic options.

- Send a sputum sample to an appropriate laboratory for culture and sensitivity. Then recall the patient when the results were available (48 hours or more later) and, if appropriate, prescribe antibiotic(s) to cover the sensitivity of the organism(s) detected. This delayed treatment and might significantly increase the severity of the condition to be treated and increase the complication rate leading to significant morbidity and even mortality.

- Empirical treatment with an antibiotic with an appropriate spectrum of activity. The most common, community acquired, bacterial causes of respiratory tract infections were: *Streptococcus pneumoniae, Haemophilus influenzae* beta lactamase (BL-), *Haemophilus influenzae* (BL+), *Moraxella catarrhalis* (BL-), *Moraxella catarrhalis* (BL+) and *Staphylococcus*

aureus. Cefaclor was active against all these bacteria, whereas a 'narrow-spectrum' antibiotic would not be. A chart containing similar information and references was included in the advertisement.

- A combination of the two options above ie obtain a sputum sample for culture and sensitivity and treat empirically. Recall the patient if the initial antibiotic was inappropriate.

In clinical practice the second and third options outlined above were almost universally followed in general practice and the approach outlined in the advertisement was consistent with good medical practice. The advertisement offered prescribers free starter packs (of 2 tablets, not 14 days of treatment) to commence treatment out-of-hours ie if they saw patients when the local pharmacy was closed. This was, again, consistent with good medical practice and offered the benefit of immediate commencement of treatment.

As a background the normal bacterial flora in the gut served as the major barrier against colonization by *C. difficile*. In general, the composition of the normal microflora was remarkably stable. The flora could be altered, however, by such factors as antimicrobial therapy, diet, pathological conditions, and gastrointestinal tract surgery. Of these, antimicrobial therapy was the most frequent cause of disturbance to the normal oropharyngeal and intestinal flora.

In a review of the pathophysiology of antibiotic-associated diarrhoea and colitis, Hooker *et al* (1988) noted that the alterations in normal gastrointestinal flora were often the result of incomplete oral absorption of antibiotics. Bergan (1986) noted in a review article that 'The better the bioavailability, i.e., the amount of oral dose reaching the systemic circulation, the less the amounts spilled into the colonic lumen. High amounts of drug within the colon would represent both an economic waste and have high potential of influencing the fecal flora'. Therefore, an antibiotic that was incompletely absorbed was likely to have a significant effect on the bowel flora.

Virtually every antibiotic could alter the gastrointestinal flora, leading to the proliferation of potentially pathogenic bacteria, such as *C. difficile.* Cefaclor, whilst having a broad spectrum of activity, was nearly 95% absorbed; in a healthy volunteer study where subjects received 750mg of Cefaclor daily for 7 days no medicine was detected in the faeces (Nord *et al* 1986).

Nord *et al* (1987) studied the impact of orally administered cefaclor, penicillin, erythromycin, bacampicillin, clindamycin, doxycycline, metronidazole, norfloxacin and ciprofloxacin on intestinal microflora. Pronounced alteration of the intestinal flora occurred in patients who received clindamycin and erythromycin, whereas only moderate changes were observed in patients who received doxycycline and ciprofloxacin. Penicillin, bacampicillin, cefaclor and metronidazole produced only minor changes in the intestinal flora.
Nord *et al* (1986), assessed the impact of cefaclor, 250mg every 8 hours, on the normal human oropharyngeal and intestinal microflora in 10 healthy adults. No marked effects on the aerobic oropharyngeal microflora were apparent. Also, no new oropharyngeal colonization occurred. Cefaclor caused only minor changes in the intestinal microflora. Anaerobic cocci decreased, while other anaerobic bacteria remained unaffected. Within 1 week post-therapy the anaerobic microflora returned to normal in all subjects. None of the volunteers experienced gastrointestinal side effects. The authors stated that with other antibiotics 'the alteration of the aerobic microflora has led to undesirable consequences such as superinfections and C. difficile intestinal diseases'. The findings in the present investigation indicated that cefaclor had minor ecological impacts on the normal human oropharyngeal and intestinal microflora.

The HPA guidance '*Clostridium difficile* infection: How to deal with the problem' stated: 'Use narrow-spectrum agents for empirical treatment where appropriate', 'Avoid use of clindamycin and second- and third-generation cephalosporins, especially in the elderly'. This document, however, presented no data on the risk of second- or third-generation cephalosporins in causing *C. difficile* infections. No references in this document reviewed this topic; the basis of the position taken in this document was another HPA document.

The HPA document '*Clostridium difficile* infection: How to deal with the problem – a board to ward approach, draft for comment' stated in Section 4 that third-generation cephalosporins had been strongly associated with *C. difficile* infection and that 'effective restriction of third generation cephalosporins was associated with a reduction in *C.difficile* infections'. The review presented no data on second-generation cephalosporins.

This review also did not refer to Levy *et al* (2000) which involved 358,389 ambulatory patients and analysed the prevalence of *C.difficile* diarrhoea (CDD) and the risk for this associated with different oral antibiotics commonly used in the ambulatory care setting. The study showed that different antibiotics were associated with varying degrees of risk for CDD eg a first-generation cephalosporin (cefalexin), and a third-generation cephalosporin (cefixime) were associated with a higher relative risk for CDD than other antibiotics assessed. There were no cases of *C.difficile* associated with cefaclor in 15,966 risk periods.

Of 8,346 patients evaluated for safety in cefaclor clinical trials, gastrointestinal reactions, especially diarrhoea, nausea or vomiting (either alone or in combination), occurred in 209 (2.5%). Cefaclor treatment was discontinued in 55 of these patients (0.6%). Two reports of gastroenteritis occurred, and there were no reports of pseudomembranous colitis (Hislop 1988).

The impact of a wide number of antimicrobial agents on the human intestinal microflora was reviewed by Nord and Edlund (1990). At recommended doses and for recommended duration of treatment only cefaclor demonstrated a lack of effect on intestinal flora. This review also supported the change in 'classification' of cefaclor from high to low risk when given at recommended doses and a recommended duration of therapy.

Given the spectrum of activity and side effect profile of cefaclor the advertisement in question was consistent with good medical practice and the scientific literature available and that specific to cefaclor itself, and did not encourage the development of unwarranted cases of *C. difficile* infection.

Flynn noted the Department of Health's (DoH's) attitude was implicit in its recent public tender for oral antibiotic stocks for reserve in anticipation of a UK H1N1 pandemic (offer reference CM/EMI/08/5034). In that tender the DoH sought offers for the supply of up to 10,690,000 courses of oral co-amoxiclav (or doxycycline), a broad-spectrum antibiotic intended for use primarily in the community. The evidence to support the use of co-amoxiclav in preference to cefaclor was unclear. In contrast, Flynn found, as was supported by the evidence described above, that cefaclor was indiscriminately presumed 'guilty' by association – in other words a class effect which was not supported by the evidence. Still further, Flynn noted, as set out in the advertisement, the evidence in support of cefaclor in preference to co-amoxiclav where gastrointestinal side effects were a concern.

PANEL RULING

The Panel noted that Flynn had offered starter packs not samples. The Code defined starter packs as a small pack designed to provide sufficient medicine for a primary care prescriber to initiate treatment when there might be an unavoidable delay in having a prescription dispensed. Antibiotics were mentioned as a type of medicine which could appropriately be given in starter packs.

The Panel considered that the mailing was confusing in that the content of the starter pack was not made clear; the starter pack offer was repeated immediately after reference to the calendar packs of 14 tablets. Flynn had submitted that the starter packs contained two tablets. Starter packs were not samples. Clauses 17.1 and 17.12 referred only to samples. Thus the Panel ruled no breach of Clauses 17.1 and 17.12.

The Panel noted that the advertisement stated that influenza might leave patients susceptible to secondary bacterial respiratory tract infections. Such patients might appreciate a free starter pack if seen out of hours or when the local pharmacy was closed. This was followed by two questions 'Do you have the time or the resources to find out which organism is responsible for your patients' secondary respiratory infections?' and 'Or do you need to prescribe a broad spectrum antibiotic which covers the most common bacterial causes?' followed by 'If so, consider Distaclor'.

The Panel noted that the complainant's PCT prescribing team discouraged the use of second- and third-generation cephalosporins in primary care as advised by the HPA and local experts. The Panel noted, however, that provided a medicine was promoted in such a way that was not inconsistent with its SPC, it was not necessarily unacceptable under the Code if that promotion was not in line with local or national guidelines.

In this instance the Panel considered that although the HPA advised against the use of, *inter alia*, second-generation cephalosporins, the advertisement at issue was not inappropriate as alleged. No breach of Clause 7.10 was ruled.

Given its rulings above the Panel did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled.

Complaint received **20 November 2009**

Case completed **9 February 2010**