CASE AUTH/2316/5/10

CONSULTANT IN PALLIATIVE MEDICINE v FLYNN PHARMA

Conduct of representative

A consultant in palliative medicine, complained about the conduct of a Flynn Pharma representative promoting Actiq (oral transmucosal fentanyl citrate). The complainant alleged that during a meeting in February the representative made false claims about Abstral [sublingual fentanyl citrate], marketed by ProStrakan; he claimed that Abstral was frequently swallowed and thus absorbed from the stomach rather than sublingually. This was neither an evidence-based statement nor true and in fact data showed Abstral had approximately 70% sublingual absorption/bioavailability. The complainant alleged that the representative also made inaccurate statements about the efficacy of Abstral.

The complainant stated that, in summary, the representative had claimed that with Actiq patients could 'turn their pain control on and off' by removing the Actiq lozenge once they achieved pain control. To the complainant's knowledge this was not evidence-based and the profile of the product did not lend itself to this. The complainant's main concern was the way the representative discussed Abstral. The representative discussed the lack of evidence for Abstral compared with Actiq which the complainant questioned.

The Authority informed the complainant that the claim that patients could 'turn their pain control on and off' with Actiq had been ruled in breach of the Code in Case AUTH/2303/3/10 and that the Director accordingly did not propose to take the matter up as a complaint. This was accepted by the complainant.

The detailed response from Flynn Pharma is given below.

The Panel noted that the complainant was concerned about what the representative had said about a competitor product, Abstral marketed by ProStrakan, in the course of promoting Actiq. Abstral was presented as a tablet for sublingual administration. The representative was reported to have stated, however, that Abstral was usually swallowed by patients and had poor bioavailability. The complainant submitted that there was no evidence to show that Abstral was swallowed and he noted that the bioavailability of Abstral was approximately 75% compared with 50% for Actiq.

The Panel noted that the Abstral summary of product characteristics (SPC) stated that the bioavailability of the product had not been studied but was estimated to be about 70%. The representative recalled telling the complainant that there was no clear published data to support the claim that Abstral's bioavailability was estimated to be 70%. According to his witness statement, it did not appear that the representative had told the complainant that the estimate of 70% was stated in the SPC. Although noting the lack of other published data the Panel nonetheless considered that the SPC contained the agreed details about a product and thus the fact that the information was included in that document gave it an official status. The SPC was a publicly available document. One slide from a presentation which Flynn used to brief its representatives about Abstral referred to the bioavailability of Actiq and Abstral and stated the 'Abstral SmPC states "The bioavailability of Abstral *has not been studied* but *is estimated* to be 70%" (how do they know – on what basis?)'. The Panel considered that by adding emphasis to the wording in the Abstral SPC and including the question 'How do they know – on what basis?', the training slide presentation disparaged Abstral. The Panel ruled a breach of the Code. In that regard the Panel considered that the briefing material would advocate a course of action which would be likely to lead to a breach of the Code. A breach of the Code was ruled.

With regard to the actual interview, the Panel noted that it was impossible to know what had transpired between the parties. The Panel noted that the complainant had generally alleged that the representative had made inaccurate statements about the efficacy of Abstral and that he had discussed the lack of evidence for Abstral compared with Actiq. No details had been provided by either party. However, given the content of the briefing material, that it appeared that the representative did not make it clear to the complainant that the estimated bioavailability of Abstral was stated in the SPC, that, according to his witness statement, the representative had appeared to question the speed of action and ease of use of Abstral and that the representative had finally advised the complainant to ask the Abstral representative for the bioavailability and efficacy data, the Panel considered that, on the balance of probabilities, the representative had misled the complainant about the competitor product. Breaches of the Code were ruled in this regard.

With regard to the allegation that the representative had stated that Abstral was usually swallowed by patients, the Panel noted that the representative had not specifically commented on it in his interview and when asked to by email three days later he stated that '… as the call was in excess of 3 months ago, unfortunately I don't have a sufficiently clear recollection to expand on the

information already provided'. The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. It was impossible to know what had transpired between the parties. Although noting that extreme dissatisfaction was usually required before an individual was moved to complain, on the basis of the information before it the Panel ruled no breach of the Code.

A consultant in palliative medicine complained about the conduct of a representative from Flynn Pharma Ltd, in relation to the promotion of Actiq (oral transmucosal fentanyl citrate).

COMPLAINT

The complainant noted that the representative visited him by appointment in February to discuss Actiq. The complainant alleged that during the meeting he made false claims about Abstral [sublingual fentanyl citrate], marketed by ProStrakan; he claimed that Abstral was frequently swallowed and thus absorbed from the stomach rather than sublingually. This was neither an evidence-based statement nor true and in fact data showed Abstral had approximately 70% sublingual absorption/bioavailability. The complainant alleged that the representative also made inaccurate statements about the efficacy of Abstral.

The complainant was concerned about the representative's professionalism on the day and had considered that his behaviour was unacceptable. The complainant had since been advised to report his concerns.

In further communication, the complainant stated that, in summary, the representative had claimed that with Actiq patients could 'turn their pain control on and off' by removing the Actiq lozenge once they achieved pain control. To the complainant's knowledge this was not evidence-based and the profile of the product did not lend itself to this. The complainant's main concern was the way the representative discussed Abstral. He provided false information about Abstral ie that it was usually swallowed by patients and had poor bioavailability when in fact the bioavailability of Abstral was much better than that of Actiq, approximately 75% compared with 50%, and there was no evidence to support his claim that the tablet was swallowed as it dissolved very fast sublingually. The representative also discussed the lack of evidence for Abstral compared with Actiq which the complainant questioned.

When writing to Flynn the Authority asked it to respond in relation to Clauses 7.2, 7.4, 8.1, 15.2 and 15.9 of the Code.

The Authority informed the complainant that the claim that patients could 'turn their pain control on and off' with Actiq had been ruled in breach of the Code in Case AUTH/2303/3/10 and that the Director accordingly did not propose to take the matter up as a complaint. This was accepted by the complainant.

RESPONSE

Flynn stated that it took all complaints seriously and none more so than when they were about a representative from a health professional. Whereas inter-company complaints might reflect a degree of competitive rivalry and positioning, in this case a health professional had felt the need to raise a matter not about promotional material content or claims, but more particularly, about professional conduct. Clearly there were implications in terms of company and individual reputation that might colour or influence a health professional's opinion about the individual, the company and the product(s).

Flynn noted that a senior manager had conducted a face-to-face interview with the representative in May. The record of that interview, signed by both parties, was provided. Clearly a little over three months had elapsed between the meeting with the complainant and the interview (and also the complaint itself) and the detail of the recollection of actual discussions and any interpretation of them needed to be viewed in that context. However, Flynn also provided a copy of the meeting record logged contemporaneously by the representative on the company's Customer Account Management system. Flynn submitted that there was nothing in either document which appeared inappropriate or gave rise to significant concerns.

The overall recollection was that the meeting went well as it resulted in the complainant providing contact information for other health professionals at the hospice.

The representative recalled that the discussion of Abstral was in response to the complainant stating that there were now a number of competitor products and that he was using Abstral. This was consistent with the representative's training insofar as Flynn's representatives were briefed not to proactively raise competitor products.

The representative made some remarks about Abstral in response to his understanding of an assertion that the product worked 'within a couple of minutes'. His response on this point was made with reference to the Abstral summary of product characteristics (SPC): significant pain relief from 15 minutes; no published data re bioavailability of Abstral; comment that Abstral took up to 30 minutes for complete absorption.

All of these points were consistent with the Abstral SPC as noted below.

Section 4.2, Posology and method of administration: 'If inadequate analgesia is not obtained within 15-30 minutes of administration of a single tablet, a second 100mcg sublingual tablet

may be administered'.

Section 5.1, Pharmacodynamic properties: 'Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes…'.

Section 5.2, Pharmacodynamic properties: 'Rapid absorption of fentanyl occurs over about 30 minutes following administration of Abstral. The bioavailability of Abstral has not been studied but is estimated to be about 70%.

Flynn submitted that given the representative's account of the meeting, his response was reasonable and measured and consistent with the Abstral SPC. Similarly, with respect to the view that a component of Abstral's absorption was via the oral route, this was consistent with the statement in Section 5.2 of the SPC.

Flynn stated that it would defend the representative's assertion about the estimate of Abstral's bioavailability at 70%. His comments were fundamentally matters of fact which Flynn did not consider were disparaging, misleading or incapable of substantiation and were offered as a relevant response to a point raised in discussion. Flynn submitted that this countered any potential breaches of Clauses 7.2, 7.4 and 8.1 of the Code. Flynn noted that the Abstral SPC stated that 'The bioavailability of Abstral has not been studied'. Indeed this was a specific point made in the technical briefing and training of Flynn's representatives as was indicated in the slide set and briefing notes provided. Flynn stated that to its knowledge, there were no specific published data which justified or clarified the bioavailability estimate for Abstral.

Flynn noted that with regard to the bioavailability of Abstral, the complainant had commented that it '… was much better than that of Actiq, approximately 75% compared with 50%,' and that 'data showed Abstral had approximately 70% sublingual absorption/bioavailability'. Given that there were no published studies setting out this position, these statements relied on the estimated 70% bioavailability reported in the Abstral SPC and/or separate unpublished comments and communications. The estimate of 50% bioavailability for Actiq came from Streisand *et al* (1991); approximately 25% came from the oromucosal absorption route and the other 25% resulted from oral absorption ie oral bioavailability was approximately 33%. Data from Streisand *et al* were given further credence by Darwish *et al* (2007) who reported the absolute and relative bioavailability of Actiq. In this study, the authors found an absolute bioavailability of 47% for Actiq and an oral bioavailability of 31% for fentanyl.

Flynn stated that if one took as a guide an assertion that the oral bioavailability of fentanyl was 33% (based on Streisand *et al*) and accepted the Abstral estimate of bioavailability as being 70%, then, to achieve this, would require that approximately 55% of the total dose of Abstral was absorbed through the oral mucosal route. If one also considered that a major benefit of the oral transmucosal delivery route for fentanyl was to achieve rapidity of (clinical) effect consistent with the temporal profile of a breakthrough pain episode, it was also reasonable to then assume that the substantial component of a product's clinical effect derived from the oromucosal absorption component of the dose.

It further seemed reasonable then that one would expect to see some correlation between the relative difference in oromucosal absorption for Actiq and Abstral and the optimum doses used in clinical trials (ie following titration) and ultimately then in the doses of the two products used in clinical practice. The available data, however, seemed to be inconsistent with this model.

Christie *et al* (1998) reported that 49% of patients did not require upward titration of Actiq from 200mcg and that 64% of patients required doses no higher than 400mcg. These proportions were very similar to those found in clinical practice as evidenced from the sales of Actiq by product strength (IMS data – not supplied) which suggested that the trial population was broadly representative of the patient population. However, the picture for Abstral was quite different – ProStrakan in Case AUTH/2207/2/09, reported that in trials, 48% of patients required doses of 600-800mcg. Flynn did not comment on the indicated Abstral dose based on IMS data as the data were more limited and confounded by the fact that for Abstral, a 'dose' was defined as one or two tablets (whereas for Actiq a dose was defined as a single lozenge).

Taking, however, the lower point of the dose range (600mcg), one was invited to accept that 48% of patients required a dose of (not less than) 600mcg. Although one must be cautious against making inferences in regard to pharmacokinetic-pharmacodynamic correlation, if the overall bioavailability of Actiq and Abstral were 50% and approximately 70% respectively and 64% of the patient population could be satisfactorily treated with doses of 200mcg or 400mcg Actiq, then it would follow that, the same population should be satisfactorily managed with doses of Abstral of ≤300mcg. If one applied the derived values for the oromucosal component of fentanyl absorption for Actiq and Abstral (of 25% and 55%, the latter figure being based on the 'estimate' of Abstral's overall bioavailability of 70% (ref SPC) and an oral bioavailability of 33% for fentanyl), and accepted that the oromucosal component contributed primarily to clinical effect, then Abstral doses of 100mcg or 200mcg would be expected to be comparable with Actiq doses of 200mcg or 400mcg. Although these arguments were somewhat theoretical, their logic was transparent and based on published data and estimates. Regardless, it was difficult on the available evidence, to reconcile the view as to Abstral's bioavailability with the trial

evidence that indicated that 48% of patients required a dose of ≤600mcg fentanyl, when Actiq trial and population data suggested a dose of 200mcg or 400mcg fentanyl was adequate to manage episodes of breakthrough cancer pain in 64% of cases.

With regard to the complainant's comments about '… [Abstral] was usually swallowed by patients and had poor bioavailability' and that 'Abstral was frequently swallowed and thus absorbed from the stomach rather than sublingually', the representative's witness statement did not address this matter and in response to a subsequent email, he was unable to recall any discussion or comment on his part in those terms. Flynn submitted that further insight was gleaned from review of its detailed briefing materials and accompanying training slide set. These were the only materials that had been briefed or supplied to Flynn's representatives about Abstral. They focussed largely on Rauck *et al* (2009) which was the only published clinical study describing Abstral. This was, however, notwithstanding that Flynn had, as yet, unresolved questions as to the formulation studied which were touched upon in a pending case, Case AUTH/2309/4/10. Regardless, the briefing document was, in Flynn's view, a balanced and entirely proper scientific analysis and critique of Rauck *et al*.

The training slide set largely followed the written briefing document. Flynn submitted that these materials provided an important reference point and refuted any suggested breach of Clause 15.9, it would be inappropriate to overly apply their teachings to a consideration of a discussion recalled and reported three months after it took place.

Flynn noted that the representative in question had a BSc in biotechnology and had worked in the pharmaceutical industry more or less continuously for 22 years. The representative joined Flynn in 2009 as part of a field-force expansion and took on representative responsibilities for Actiq in October 2009 pursuant to a commercial agreement between Cephalon and Flynn regarding UK sales and marketing responsibilities for Actiq. The representative had passed his ABPI examination.

Flynn stated that there was little doubt that the representative was highly experienced and appropriately qualified. This was the first complaint about his professional conduct in a 22-year career in pharmaceutical sales and marketing and he was understandably concerned and upset to be the subject of complaint. His career experience, unblemished record and personal integrity should, and did, feature in Flynn's assessment and response to the particulars of this case.

With regard to a potential breach of Clause 15.2 (high standards and professional conduct) Flynn submitted that its difficulty was the 'evidence' in considering this point and, indeed, any case where it turned on a discussion. However, to the extent that the complainant had felt cause to register a complaint, there was an 'issue' and this was something Flynn wished to resolve. Therefore, the company's position was, simply, that if the complainant genuinely felt after reviewing the above that there was 'unacceptable behaviour', then Flynn would consider accepting a ruling of a breach of Clause 15.2. Irrespective of the abovementioned arguments and the good character and record of the representative, who Flynn considered acted professionally and with good and proper intent, if offence had been caused the company would accept that at face value and without dispute.

PANEL RULING

The Panel noted that Flynn had agreed for its response to be sent to the complainant for comment before the Panel made its ruling. The Panel, however, considered that in this case such action was not necessary and it made its ruling based on the initial submissions by both parties.

The Panel noted that the complainant was concerned about what the representative had said about a competitor product, Abstral marketed by ProStrakan, in the course of promoting Actiq. Abstral was presented as a tablet for sublingual administration. The representative was reported to have stated, however, that Abstral was usually swallowed by patients and had poor bioavailability. The complainant submitted that there was no evidence to show that Abstral was swallowed and he noted that the bioavailability of Abstral was approximately 75% compared with 50% for Actiq.

The Panel noted that the Abstral SPC stated that the bioavailability of the product had not been studied but was estimated to be about 70%. The representative recalled telling the complainant that there was no clear published data to support the claim that Abstral's bioavailability was estimated to be 70%. According to his witness statement, it did not appear that the representative had told the complainant that the estimate of 70% was stated in the SPC. Although noting the lack of other published data the Panel nonetheless considered that the SPC contained the agreed details about a product and thus the fact that the information was included in that document gave it an official status. The SPC was a publicly available document. In a training slide presentation which Flynn used to brief its representatives about Abstral, slide 16 referred to the bioavailability of Actiq and Abstral. The statement about Abstral read 'Abstral SmPC states "The bioavailability of Abstral ***has not been studied*** but ***is estimated*** to be 70%" (how do they know – on what basis?)'. The Panel considered that by adding emphasis to the wording in the Abstral SPC and including the question 'How do they know – on what basis?', the training slide presentation disparaged Abstral. The Panel ruled a breach of Clause 8.1. In that regard the Panel considered that the briefing material would advocate a course of action which would be likely to lead to a breach of

the Code. A breach of Clause 15.9 was ruled.

With regard to the actual interview, the Panel noted that it was impossible to know what had transpired between the parties. The Panel noted that the complainant had generally alleged that the representative had made inaccurate statements about the efficacy of Abstral and that he had discussed the lack of evidence for Abstral compared with Actiq. No details had been provided by either party. However, given the content of the briefing material, that it appeared that the representative did not make it clear to the complainant that the estimated bioavailability of Abstral was stated in the SPC, that, according to his witness statement, the representative had appeared to question the speed of action and ease of use of Abstral and that the representative had finally advised the complainant to ask the Abstral representative for the bioavailability and efficacy data, the Panel considered that, on the balance of probabilities, the representative had misled the complainant about the competitor product. Breaches of Clauses 7.2 and 15.2 were ruled in this regard.

With regard to the allegation that the representative had stated that Abstral was usually swallowed by patients, the Panel noted that the representative had not specifically commented on it in his interview and when asked to by email three days later he stated that '… as the call was in excess of 3 months ago, unfortunately I don't have a sufficiently clear recollection to expand on the information already provided'. The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. It was impossible to know what had transpired between the parties. Although noting that extreme dissatisfaction was usually required before an individual was moved to complain, on the basis of the information before it the Panel ruled no breach of Clauses 7.2 and 7.4 of the Code.

During its consideration of this matter the Panel noted that slide 11 of the training slide presentation was headed 'Protocol Violations or Withdrawal of Consent. The slide, *inter alia*, stated that the study protocol in Rauck *et al* was difficult to adhere to because the tablet had to be placed 'under tongue in deepest part of the oral cavity and allow to dissolve, **without chewing sucking or swallowing the medication**'. The Panel noted that the competitor briefing document which detailed the findings of Rauck *et al* stated that one hypothesis for protocol violation or withdrawal of consent was that the '… study protocol was difficult to adhere to – if, for example patients were asked not to swallow for up to ten minutes to ensure effective sublingual absorption'. The Panel could not find this instruction anywhere in the published paper. The published paper stated that patients were instructed not to chew, suck or swallow the medication. It thus appeared from the briefing documents that difficulty in using the tablets was a major reason for protocol violation. The Panel, however, noted that although Rauck *et al* reported that a number of patients were withdrawn from the study due to 'protocol violation', no reasons for the violations were given. The Abstral SPC stated in Section 5.2 that Abstral was a quick dissolving sublingual tablet formulation. Rapid absorption of fentanyl occurred over about 30 minutes following administration. Rauck *et al* stated that sublingual fentanyl might provide additional benefits to patients as it was a small discreet tablet that did not require a delivery device or patient manipulation once it had been placed under the tongue; however, the impact of these properties had not been evaluated in a real-life setting. The Panel considered that the training slide and briefing document disparaged Abstral; they implied that patients would find the tablets difficult to take properly but there was no data to support this. The Panel requested that Flynn be advised of its concerns in this regard.

The Panel noted that the competitor briefing document under the heading 'Limitations of the Study' put forward a number of hypotheses to explain the reasons for protocol violation or withdrawal of consent from Rauck *et al* including 'To reduce the number of patients withdrawing from the study because of lack of efficacy or adverse events'. The Panel considered that the reasons put forward were conjecture on Flynn's part and in that regard disparaged Abstral. The Panel requested that Flynn be advised of its concerns in this regard.

Complaint received **7 May 2010**

Case completed **1 July 2010**