CASE AUTH/2303/3/10

PROSTRAKAN v FLYNN PHARMA

Promotion of Actiq

ProStrakan complained about an Actiq (oral transmucosal fentanyl citrate) leavepiece and a journal advertisement both issued by Flynn Pharma. Actiq was indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain.

ProStrakan stated that both pieces referred to pain control and featured the claim 'She needs to turn it on when it starts … and off when it's finished'. 'On' and 'off' were in bold and highlighted in colour ['on' was in green; 'off' was in red].

According to the recent Association for Palliative Medicine guidelines (Davies *et al* 2008), breakthrough pain was characterised by acute onset and short duration (median 30 minutes).

The Actiq summary of product characteristics (SPC) stated that significant analgesia was achieved from 15 minutes following administration. ProStrakan alleged it was therefore inconsistent with the SPC to state or imply that the analgesic effect of Actiq could be 'turned on' when pain started as the SPC stated this would take 15 minutes. Additionally, the SPC stated that T_{max} was around 20 to 40 minutes after consumption of an Actiq unit (range 20 – 480 minutes) and the terminal elimination half-life was about 7 hours. ProStrakan therefore alleged it was misleading to imply that Actiq could be 'turned off' at the end of a breakthrough pain episode that was likely to last only 30 minutes.

ProStrakan was further concerned that the leavepiece featured a photograph of a woman using an Actiq lozenge; she appeared relaxed and not to be in any pain. The Actiq SPC stated that the lozenge should be consumed over a 15 minute period. During this period a patient would not be expected to derive significant analgesia as this took at least 15 minutes to occur. ProStrakan alleged that the image was therefore misleading.

The detailed submission from Flynn is given below.

The Panel disagreed with Flynn's submission that published clinical literature took precedence over the pharmacokinetic data in the SPC. Whatever was in the published literature, product claims must not be inconsistent with the SPC. The Panel also disagreed with Flynn's statement that the claim 'she needs to turn it on when it starts… and off when it's finished' could be regarded as a general statement as to the desirable qualities of a therapy for breakthrough cancer pain. The claim was in promotional material for Actiq and thus inextricably linked to that product.

The Panel noted that Actiq was intended for oromucosal administration. The SPC stated that it should be placed in the mouth against the cheek and moved around using the applicator. The unit was to be consumed over a 15 minute period. During titration if adequate analgesia was not obtained within 15 minutes after the patient completed consumption of a single unit a second one of the same strength could be consumed. Section 5.2 of the SPC stated that T_{max} was around 20 to 40 minutes after consumption of an Actiq unit.

The advertisement and the leavepiece had a photograph of a distressed woman beside which was the claim 'she needs to turn it on when it starts' ('on' was in green and phrase was followed by the picture of a green control button) '… and off when it's finished' ('off' was in red and the phrase was followed by the picture of a red control button). The claim 'Breakthrough Cancer Pain Control' appeared beneath the photograph. The word pain was in red and control was in green.

The Panel considered that the use the pictures of control buttons similar to those found on a television etc implied that the use of 'on' and 'off' in the advertisement ie the switching of pain control on and off with Actiq, was similar to turning an electrical appliance on or off. This was not so. According to the SPC, Actiq produced significantly more breakthrough pain relief compared with placebo at 15, 30, 45 and 60 minutes. Christie *et al* (1998) demonstrated the greatest difference in pain relief in the first 30 minutes which was consistent with the advice given in the SPC regarding the titration of doses. The Panel did not consider that pain control could be turned on and off as implied. When a patient chose to treat their breakthrough pain with Actiq the analgesia would at first increase with time, until pain control was achieved, and then fade with time according to the pharmacokinetics of the medicine. The patient could not turn it on or off at will.

The Panel considered that the claim that pain control could be switched on was inconsistent with the particulars listed in the SPC. The claim that pain control could be switched off was misleading. Breaches of the Code were ruled.

The Panel noted that the front page of the leavepiece featured the black and white photograph of the woman in pain as described above. Three colour photographs on the inside of the leavepiece were clearly of the same woman who appeared relaxed and not in pain. The Actiq

lozenge was not shown in the photographs nor any indication of the time it would take to achieve pain control. The Panel did not consider that the photographs were misleading as alleged; they appeared to show a patient who had been successfully treated with Actiq such that her breakthrough cancer pain was controlled and no longer caused distress. No breach was ruled.

ProStrakan Group plc complained about the promotion of Actiq (oral transmucosal fentanyl citrate) by Flynn Pharma Ltd. The items at issue were an advertisement in the International Journal of Palliative Nursing, December 2009 (ref ACT1709) and a leavepiece (ref ACT0709). It had not been possible to resolve the issues through inter-company dialogue. ProStrakan supplied Abstral (sublingual fentanyl citrate).

Actiq was indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain.

COMPLAINT

ProStrakan stated that both pieces referred to pain control and featured the claim 'She needs to turn it on when it starts … and off when it's finished'. In both pieces, the words 'on' and 'off' were in bold and highlighted in colour ['on' was in green; 'off' was in red].

According to the recent Association for Palliative Medicine guidelines (Davies *et al* 2008), breakthrough pain was characterised by acute onset and short duration (median 30 minutes). ProStrakan noted that the Actiq summary of product characteristics (SPC) stated that significant analgesia was achieved from 15 minutes following administration. ProStrakan alleged it was therefore inconsistent with the information in the SPC to state or imply that the analgesic effect of Actiq could be 'turned on' when pain started as the SPC stated this would take 15 minutes. ProStrakan alleged a breach of Clause 3.2. Additionally, the Actiq SPC stated that T_{max} was around 20 to 40 minutes after consumption of an Actiq unit (range 20 – 480 minutes) and that the terminal elimination half-life after Actiq administration was about 7 hours. ProStrakan alleged that it was thus misleading to imply that the action of Actiq could be 'turned off' at the end of a breakthrough pain episode that was likely to last only 30 minutes, in breach of Clause 7.2.

ProStrakan was further concerned that the leavepiece featured a photograph of a woman using an Actiq lozenge. The woman appeared relaxed, almost smiling and was reading a magazine; she did not appear to be in any pain. The Actiq SPC stated that the lozenge should be consumed over a 15 minute period. During this period a patient would not be expected to derive significant analgesia as this took at least 15 minutes to occur. ProStrakan alleged that the image was therefore misleading, in breach of Clause 7.8.

RESPONSE

In relation to the alleged breach of Clause 3.2, Flynn noted that ProStrakan was concerned that the claim 'She needs to turn it on when it starts .... and off when it's finished', was in breach of the Code, based on its reading of the Actiq SPC and specifically:

- 'Significant analgesia is achieved **from** (emphasis added) 15 minutes following administration'
- 'Tmax is around 20 to 40 minutes after consumption of an Actiq unit (range 20 – 480 minutes)'
- 'The terminal elimination half-life after Actiq administration is about 7 hours'.

Whilst the second and third statements were accurate quotations from the SPC (Section 5.2), the first was not. The actual statement in the SPC (also Section 5.2) to which ProStrakan referred read as follows:

> 'In patients with chronic cancer pain on stable doses of regularly scheduled opioids to control their persistent pain, Actiq produced significantly more breakthrough pain relief compared with placebo **at** (emphasis added) 15, 30, 45, and 60 minutes following administration.'

To a large extent ProStrakan's interpretation and position turned on its incorrect use and substitution of 'from' in place of 'at'. It was also a further error and misrepresentation of the facts and evidence by ProStrakan when it asserted 'a patient would not be expected to derive significant analgesia as this takes **at least** (emphasis added) 15 minutes to occur'. ProStrakan had thus moved from the facts of 'at 15 minutes' to 'from 15 minutes' and finally to 'at least 15 minutes', and in so doing, materially misrepresented and changed the meaning of the relevant statement in the Actiq SPC. Flynn was particularly concerned that, having drawn ProStrakan's attention to these errors of fact in inter-company correspondence, ProStrakan had ignored the point and repeated an inaccurate and invalid allegation. These matters could surely have been checked and corrected having been highlighted previously to ProStrakan?

Quite simply 'at', 'from' and 'at least' had different meanings and particular relevance to interpretation of the SPC statement in question.

The wording 'at 15 minutes' as included in the SPC meant in or near, within the interval or span of, on, near, or by the time of (15 minutes). In contrast if 'from' was substituted in place of 'of', the meaning of the statement was changed to mean or indicate a separation, differentiation or exclusion, or a specified point as the first of a number of points (from 15 minutes). When the word substitution was taken further to use 'at least' in place of 'at', the statement was altered still further from the original. Thus one now had an interpretation of 'this takes at

least 15 minutes to occur' such that the reader might think that the analgesia occurred at not less than 15 minutes or that the 15 minute time point was the earliest possible time point of importance, magnitude or degree.

In short, the meaning of the cited SPC statement had been materially altered and Flynn found it mischievous of ProStrakan to have done so given Flynn had previously pointed out the errors of fact.

In support of the alleged breach, ProStrakan had also referred to Davies *et al* and specifically the statement that breakthrough pain was characterised by its acute onset and short duration (median 30 minutes). Davies *et al* relied on Portenoy and Hagen (1990) in quoting the median duration of a pain episode as 30 minutes. Portenoy and Hagen and also Davies *et al* went further in reporting the range of duration of a typical pain episode as 1-240 minutes. The median was no more than the middle value in the distribution of durations of pain episodes studied. There would thus be an equal number of pain episodes of less than 30 minutes as there would be episodes of longer than 30 minutes, and they were all included within the range of 1 -240 minutes. This was hardly consistent with ProStrakan's assertion that a breakthrough pain episode was likely to last only 30 minutes. Portenoy and Hagen showed quite clearly that this was not the case. It would follow therefore that an analgesic intervention that lasted only 30 minutes would fail to treat to a greater or lesser extent, up to half of all pain episodes. Based on Portenoy and Hagen (on which Davies *et al* relied), one would ideally wish to have an analgesic intervention that lasted in clinical effect up to 240 minutes to treat all pain episodes.

Actiq had been shown to produce significantly different pain relief at 15 minutes, this time-point being the first one at which the pain intensity difference (PID) and the pain relief (PR) scores were recorded by Christie *et al* (1998) which provided supporting evidence to underpin this statement. Christie *et al* was a supporting reference included in the leavepiece and advertisement. Review of the detail of the paper and specifically Figure 3 provided the evidence. Flynn submitted that it was reasonable to assume that the PID and PR plots had a linear relationship vs time between successive time intervals given that neither variable could be continually measured. Certainly it was more realistic than ProStrakan's position, that given that 15 minutes was the first interval at which PID and PR were measured to the effect or meaning that 'significant analgesia is achieved from 15 minutes'. Equally it was implausible to adopt the view that there was no relief in the period up to 15 minutes and that instant relief was experienced at and beyond 15 minutes. Clearly many patients, if not the majority, would experience increasing pain relief and benefit in the period leading up to 15 minutes.

Another study (Portenoy *et al* 1999) cited in the advertisement, added more weight and evidence in support of Flynn's position. Portenoy reported that 65% of the total pain relief with Actiq occurred within the first 15 minutes. Also in further support and substantiation of the claims set out in the advertisement, Flynn had cited Farrar *et al* (1998). Consistent with the reported findings of Christie *et al*, Farrar *et al* recorded a significant difference between Actiq and placebo in PID and PR scores measured at 15 minutes.

Yet another published study, although not relied on or cited in the material at issue, was an open-label study which evaluated 10 in-patients with breakthrough cancer pain that was not well controlled with their current therapies (Fine *et al* 1991). This study provided experience of 42 Actiq dose administrations and employed a pain questionnaire to provide assessments of pain and relief at 5, 10, 20, 30, 60 and 120 minutes after administration. Onset of analgesia was defined as the time interval between **initiation** (emphasis added) of Actiq administration and notification of pain relief by the patient. Significant and clinically relevant reductions in pain scores were seen at all evaluations from 5 to 120 minutes and the average time of pain relief onset was 9.5 minutes. Indeed, based on the findings of Fine *et al*, it would not be unreasonable to claim meaningful pain relief within ten minutes.

Whilst the previous comments in response to the alleged breach of Clause 3.2 addressed the question of 'turning it on when it starts', they had some relevance to the question of 'turning it off' (when it was finished) which was central to the alleged breach of Clause 7.2.

ProStrakan had postulated that if T_{max} was 20-40 minutes after consumption of an Actiq unit (range 20 – 480 minutes), and that the terminal elimination half-life after Actiq administration was about 7 hours, it was then inconsistent or misleading to imply that the action of Actiq could be 'turned off' at the end of a breakthrough pain episode that was likely to last only 30 minutes.

The data and SPC for Actiq showed that T_{max} typically occurred in 20-40 minutes from the start of dosing, and theoretically 5-25 minutes after onset of the breakthrough cancer pain episode if taken immediately (and accepting that the time to complete administration of a single lozenge was 15 minutes). However Flynn submitted that the published clinical literature, discussed in relation to the alleged breach of Clause 3.2, took precedence over the pharmacokinetic data and better informed readers as to product performance.

Although ProStrakan had commented on the terminal elimination half-life after administration of Actiq, Flynn was unclear as to its relevance to the product claims at issue or the extent if at all, that it supported the alleged breach. Flynn failed to see the significance of metabolism and elimination kinetics to questions around onset of action. It was not the terminal half-life that was important, but the rate of decay from peak levels ie approximately 20

minutes. Side effects were opioid related and dose dependent. The formulation of Actiq (lozenge on a stick) allowed removal of a partially completed dose if the patient experienced side effects. This was an important, unique and differentiating characteristic of the Actiq dose form in the therapy area.

As to the validity of the 'She needs to turn it **on** when it starts…. and **off** when it is finished' strapline, Flynn believed ProStrakan had misrepresented and misinterpreted the Actiq SPC. Flynn agreed that the onset of breakthrough cancer pain was often sudden and its duration could be short (but as Portenoy and Hagen found there was a considerable range or spread in duration). The most effective therapy then was one that had a short duration of onset and an appropriately short duration of action. To that extent, the evidence supported the claims that Actiq would provide analgesia at 15 minutes after initiation of treatment.

Equally, the claim could be regarded as a general statement as to the desirable qualities of a breakthrough cancer pain therapy, rather than a comment which exclusively applied to Actiq. It was the properties of fentanyl itself that were most pertinent to the switching 'off'. Flynn noted that the British National Formulary (BNF) 58 (September 2009) stated that fentanyl was 'particularly useful because it acts within 1-2 minutes and has a short duration of action'. Whilst the speed of onset referred to a systemic route of delivery, once it was inside the body, its subsequent distribution, metabolism and excretion were largely independent of route of administration. Fentanyl was considered a 'short-acting' medicine and was often given as a continuous infusion because of these properties. When the administration was stopped, whether this be discontinuation of an infusion, removal of a partially consumed lozenge, or on completion of a dose, its clinical effects and potential for adverse effects would quickly dissipate. This was the meaning behind 'turning it off when it's finished'. Indeed, Flynn suggested a similar claim might be made of certain other available fentanyl.

Flynn noted that with regard to the alleged breach of Clause 7.8, ProStrakan had taken issue with the picture in the leavepiece of a woman reading a magazine who appeared relaxed, almost smiling and not in pain.

ProStrakan stated correctly from the SPC that the lozenge should be consumed over a 15 minute period. However ProStrakan was wrong to assert that 'During this period a patient would not be expected to derive significant analgesia as this takes at least 15 minutes to occur'. Portenoy *et al* rebutted this position – 65% of the total pain relief with Actiq occurred within the first 15 minutes. Thus it was entirely reasonable and consistent with the data to express a view in imagery or text, suggestive of a patient using Actiq in the licensed way, who experienced meaningful analgesia and pain relief within 15 minutes of initiation of a dose. One could even argue based on Portenoy *et al* that this was the more likely position.

This image showed a patient who had received pain relief and was able to undertake activities in the absence of uncomfortable pain. This was the goal of treatment and the proven benefit of Actiq as evidenced by the literature and a multiyear history of successful use.

In summary, Flynn refuted all three of the breaches alleged. Flynn had set out the facts as to what was and was not included in the SPC, the specific evidence used to support its claims and further literature that added weight to those claims. The majority of patients would experience pain relief before and beyond 15 minutes. The patient images did not include or refer to a timescale – they simply showed a patient not in pain and to a large extent it was irrelevant and hypothetical to debate how long before such a patient had experienced a pain episode and/or taken a dose of Actiq.

PANEL RULING

The Panel noted Flynn's submission that published clinical literature took precedence over the pharmacokinetic data in the SPC. This was not so. Whatever was in the published literature, claims made for a product must not be inconsistent with the particulars listed in the SPC. The Panel also disagreed with Flynn's statement that the claim 'she needs to turn it on when it starts… and off when it's finished' could be regarded as a general statement as to the desirable qualities of a therapy for breakthrough cancer pain. The claim was in promotional material for Actiq and given the context in which it was used it would appear to be inextricably linked to that product.

The Panel noted that Actiq was intended for oromucosal administration. The SPC stated that it should be placed in the mouth against the cheek and moved around using the applicator. The unit should be sucked and was to be consumed over a 15 minute period. The SPC stated that during titration if adequate analgesia was not obtained within 15 minutes after the patient completed consumption of a single unit a second one of the same strength could be consumed.

Section 5.1 of the SPC stated that Actiq produced significantly more breakthrough pain relief compared with placebo at 15, 30, 45 and 60 minutes following administration. Christie *et al* showed that the analgesic effect of Actiq was apparent at 15 minutes and further increased at 30 minutes. Although analgesia had increased again at 60 minutes the efficacy/time curve had begun to flatten out between 30 and 60 minutes. Section 5.2 of the SPC stated that T_{max} was around 20 to 40 minutes after consumption of an Actiq unit.

The advertisement and the leavepiece had a photograph of a distressed woman beside which was the claim 'she needs to turn it on when it starts' ('on' was in green and phrase was followed by the

picture of a green control button) '… and off when it's finished' ('off' was in red and the phrase was followed by the picture of a red control button). The claim 'Breakthrough Cancer Pain Control' appeared beneath the photograph. The word pain was in red and control was in green.

The Panel considered that the use the pictures of control buttons similar to those found on a television or other electrical appliances implied that the use of 'on' and 'off' in the advertisement ie the switching of pain control on and off with Actiq, was similar to turning an electrical appliance on or off. This was not so. According to the SPC, Actiq produced significantly more breakthrough pain relief compared with placebo at 15, 30, 45 and 60 minutes. Christie *et al* demonstrated the greatest difference in pain relief in the first 30 minutes which was consistent with the advice given in the SPC regarding the titration of doses. The Panel did not consider that pain control could be turned on and off as implied. Clearly when a patient chose to treat their breakthrough pain with Actiq the analgesia would at first increase with time, until pain control was achieved, and then fade with time according to the pharmacokinetics of the medicine. The patient could not turn it on or off at will.

The Panel considered that the advertisement and the leavepiece misleadingly implied that pain control with Actiq could be turned on and off instantaneously in a similar way to turning an electrical appliance on and off. The claim that pain control could be switched on was inconsistent with the particulars listed in the SPC. A breach of Clause 3.2 was ruled. The claim that pain control could be switched off was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the front page of the leavepiece featured the black and white photograph of the woman in pain as described above. The three colour photographs at issue on the inside of the leavepiece were clearly of the same woman who appeared relaxed and not in pain. The Actiq lozenge was not shown in the photographs nor any indication of the time it would take to achieve pain control. The purpose of including the red and green on and off control buttons beneath the photographs was not clear. However the Panel did not consider that the photographs were misleading as alleged; they appeared to show a patient who had been successfully treated with Actiq such that her breakthrough cancer pain was controlled and no longer caused distress. No breach of Clause 7.8 was ruled.

Complaint received **9 March 2010**

Case completed **22 April 2010**