CASE AUTH/2216/3/09

PROSTRAKAN v CEPHALON

Promotion of Effentora

ProStrakan complained about a 'Titration Guidelines' booklet to support the promotion of Effentora (fentanyl buccal tablet) by Cephalon. ProStrakan marketed Abstral (sublingual fentanyl citrate tablet). Effentora and Abstral were used to treat breakthrough cancer pain (BTcP) in patients already receiving maintenance opioid therapy.

The detailed response from Cephalon is given below.

The front cover of the booklet featured the claim 'A dose for each BTcP patient With a range of 5 doses, Effentora allows you to individualise the treatment of BTcP'. ProStrakan submitted that the published data for Effentora showed that a significant proportion of patients that entered the titration phase would fail to successfully complete titration. For example, Zeppetella *et al* 2008 showed that of 248 patients who commenced titration, 84 did not successfully complete the titration process. ProStrakan therefore alleged that the claim 'A dose for each patient' was inaccurate and could not be substantiated.

The Panel noted that the Effentora summary of product characteristics (SPC) stated that Effentora should be individually titrated to an effective dose that provided adequate analgesia and minimised undesirable effects. Details were given including the ability to titrate upwards as necessary through the range of available strengths.

The Titration Guidelines booklet included instructions for treatment of five BTcP episodes. The page showing the 5th BTcP episode stated that if inadequate analgesia was obtained 30 minutes after 800mcg then alternative treatment options were needed.

The Panel noted the Zepetella *et al* had combined data from two published studies of fentanyl buccal tablets in opioid-tolerant cancer patients with breakthrough pain. Of the 252 patients enrolled, 66% (167) were successfully titrated to an effective dose. For the full analysis set (n=150) the successful doses were 100mcg (9%), 200mcg (13%), 400mcg (22%), 600mcg (21%) and 800mcg (35%). In the Panel's view the data demonstrated that different patients might require up to an 8 fold difference in dose but that with five tablet strengths available prescribers had flexibility as to the dose prescribed.

The Panel noted that not all of the patients enrolled in Zeppetella *et al* were successfully treated with fentanyl buccal tablets and in the open label dose titration phase 28 (11%) dropped out due to lack of efficacy. Nonetheless, the Panel did not consider that in the context of analgesia prescribers would assume that the claim 'A dose for each BTcP patient' meant that Effentora was effective in all patients; no medicine was effective in everybody. The remainder of the claim 'With a range of 5 doses Effentora allows you to individualise the treatment of BTcP' provided further context.

Overall, the Panel did not consider that the claim 'A dose for each BTcP patient' was inaccurate as alleged or could not be substantiated. No breaches of the Code were ruled.

ProStrakan alleged that a descending scale on the front cover of the booklet implied that Effentora resulted in complete pain relief within 10 minutes and was reinforced by the scale being superimposed on an image of two people who were clearly not in any pain. The published data for Effentora showed that there was a statistically significant pain intensity difference vs placebo from 10 minutes but it did not show that patients would be pain free within this time. ProStrakan alleged that the graphic was in breach of the Code as it misled as to the efficacy of Effentora.

The Panel noted a statement in the SPC that statistically significant improvements in pain intensity difference was seen with Effentora vs placebo as early as ten minutes in one study and as early as fifteen minutes (earliest time point measured) in another study.

The Panel noted that on the front cover of the booklet the descending scale started with 10 minutes and a 9mm vertical red line at the left hand side. Thereafter each regressive minute was marked with vertical red lines which gradually decreased in height until at zero, on the right hand side, there was no red line at all. In the Panel's view this implied that whatever was present at 10 minutes was completely gone at zero. Given its inclusion in a promotional piece about Effentora, the Panel considered that some readers would assume that the sliding scale meant that Effentora produced complete pain relief in 10 minutes which was not so. The graphic was superimposed over a visual of a couple looking relaxed and happy. The Panel considered that the descending scale misled as to the efficacy of Effentora as alleged. A breach of the Code was ruled.

The company logo and strapline 'deliver more' appeared in the lower left hand corner of the front cover of the booklet. The product logo was in the

lower right hand corner. ProStrakan stated that the company logo was adjacent to the product logo and on the front cover of an Effentora promotional item. 'Deliver more' was therefore a hanging comparison in breach of the Code.

The Panel considered that the corporate logo was sufficiently separated from the product logo such that 'deliver more' would not be regarded as a claim for Effentora. No breach of the Code was ruled.

For each titration dose (100mcg/200mcg/400mcg/600mcg and 800mcg) the booklet featured diagrams of a patient's face with tablets superimposed around the jaw line. ProStrakan noted that the graphics indicated the required positioning of tablets for all doses. The images for the 600mcg (3x200mcg tablets) and 800mcg (4x200mcg tablets) doses clearly showed some tablets in the upper part of the mouth and some in the lower part of the mouth (particularly the 3x200mcg image). The Effentora SPC stated that tablets should be placed in the upper part of the buccal cavity. Thus, the information in the dose titration guide was inconsistent with the particulars in the SPC, in breach of the Code. ProStrakan was concerned that this discrepancy might pose a safety hazard for patients.

The Panel considered that the images were misleading. Where more than two tablets were to be used (ie 600mcg and 800mcg doses) some of the tablets were placed on the diagram such that they appeared over the lower buccal cavity. The SPC clearly stated that tablets were to be placed in the upper portion of the buccal cavity (above an upper rear molar between the cheek and gum). The Panel considered that the images were inconsistent with the particulars listed in the Effentora SPC. A breach of the Code was ruled.

ProStrakan noted that the prescribing information on the inside back covers of the booklet did not list the frequency of the application site reactions. According to the SPC these were 'very common' and so this information should have been included. The frequency of other adverse events was listed, therefore this omission appeared to be trying to minimise the significance of application site reactions.

The Panel noted that one of the elements of prescribing information listed in the Code was 'a succinct statement of common side-effects likely to be encountered in clinical practice'. The prescribing information at issue stated 'Application site reactions including pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles' but did not attribute any frequency to these side-effects. The Effentora SPC listed these effects as being very common. Immediately following the statement regarding application site reactions the prescribing information stated 'Very common effects (>10%) – nausea and dizziness. Common (<1%-10%) – Dysgensia, Somnolence …'. Given that frequencies of other adverse events had been stated it thus appeared that application site reactions occurred at a frequency that was something other than very common or common which was not so. To state the frequency for some adverse events but not for others was not helpful. Nonetheless the information listed in the Code had been provided and so no breach of the Code was ruled.

ProStrakan Group Plc complained about the promotion of Effentora (fentanyl buccal tablet) by Cephalon Limited. The material at issue was a 'Titration Guidelines' booklet (ref CE/FE-08031/Dec08). ProStrakan marketed Abstral (sublingual fentanyl citrate tablet). Effentora and Abstral could be used to treat breakthrough cancer pain (BTcP) in patients already receiving maintenance opioid therapy.

1 Claim 'A dose for each BTcP patient'

The front cover of the booklet featured the claim 'A dose for each BTcP patient With a range of 5 doses, Effentora allows you to individualise the treatment of BTcP'.

COMPLAINT

ProStrakan submitted that the published data for Effentora showed that a significant proportion of patients that entered the titration phase would fail to successfully complete titration. For example, Zeppetella *et al* 2008 showed that of 248 patients who commenced titration, 84 did not successfully complete the titration process. ProStrakan therefore alleged that the claim 'A dose for each patient' was in breach of Clause 7.2 of the Code as it was inaccurate and was also a breach of Clause 7.4 as it could not be substantiated.

RESPONSE

Cephalon did not dispute that a proportion of patients entering the titration phase would not achieve an effective dose. However, within the context of the process of titration (as outlined in the Titration Guidelines booklet), this was completed by the statement 'With a range of 5 doses, Effentora allows you to individualise the treatment of BTcP'.

The claim at issue referred to using the range of tablet strengths to find a suitable dose, to individualise the dose for each patient during the titration phase. For all patients for whom the decision had been made to prescribe Effentora, the essence of titration required that each patient received a dose, to establish their effective maintenance dose.

The reference quoted was consistent with other

studies on successfully completing titration. This figure was not dissimilar to general response rates with many commonly prescribed medicines.

Cephalon contended that, based on these points, the claim was not inaccurate and so not in breach of Clause 7.2; the alleged breach of Clause 7.4 was not applicable.

PANEL RULING

The Panel noted that the Effentora summary of product characteristics (SPC) stated that Effentora should be individually titrated to an effective dose that provided adequate analgesia and minimised undesirable effects. Details were given including the ability to titrate upwards as necessary through the range of available strengths.

The Titration Guidelines booklet included instructions for treatment of five BTcP episodes. The page showing the 5th BTcP episode stated that if inadequate analgesia was obtained 30 minutes after 800mcg then alternative treatment options were needed.

The Panel noted the Zepetella *et al* had combined data from two published studies of fentanyl buccal tablets in opioid-tolerant cancer patients with breakthrough pain. Of the 252 patients enrolled, 66% (167) were successfully titrated to an effective dose. For the full analysis set (n=150) the successful doses were 100mcg (9%), 200mcg (13%), 400mcg (22%), 600mcg (21%) and 800mcg (35%). In the Panel's view the data demonstrated that different patients might require up to an 8 fold difference in dose but that with five tablet strengths available the prescribers had flexibility as to the dose prescribed.

The Panel noted that not all of the patients enrolled in Zeppetella *et al* were successfully treated with fentanyl buccal tablets and in the open label dose titration phase 28 (11%) dropped out due to lack of efficacy. Nonetheless, the Panel did not consider that in the context of analgesia prescribers would assume that the claim 'A dose for each BTcP patient' meant that Effentora was effective in 100% of patients; no medicine was effective in everybody. The remainder of the claim 'With a range of 5 doses Effentora allows you to individualise the treatment of BTcP' provided further context.

Overall, the Panel did not consider that the claim 'A dose for each BTcP patient' was inaccurate as alleged or could not be substantiated. No breaches of Clauses 7.2 and 7.4 respectively were ruled.

2 Descending scale of 10 minutes to zero

The front cover of the booklet included a descending scale marked '10 minutes' with a 9mm vertical red line at the left hand side and 'O' with no vertical red line at the right hand side.

COMPLAINT

ProStrakan alleged that the descending scale clearly implied that Effentora resulted in complete pain relief within 10 minutes. This implication was reinforced by the scale being superimposed on an image of two people who were clearly not in any pain. The published data for Effentora showed that there was a statistically significant pain intensity difference vs placebo from 10 minutes but it did not show that patients would be entirely pain free within this time. ProStrakan alleged that the graphic was in breach of Clause 7.8 of the Code as it misled as to the efficacy of Effentora.

RESPONSE

Cephalon submitted that the 10 minute scale was not associated with any claim or indications that complete pain relief was achieved within 10 minutes. The implication of an association with 'complete pain relief' was only alleged by ProStrakan. The scale only highlighted 10 minutes, with otherwise the period divided into minutes without providing any further information. The 10 minutes represented an artistic interpretation at which statistical significance for numerous end-points was achieved (in a placebo-controlled trial, Slatkin *et al,* 2007). No other meaning was given to the scale.

Cephalon contended in view of the fact that the images, individually or in combination, did not indicate patients were entirely pain free within 10 minutes the alleged breach of Clause 7.8 was unfounded.

PANEL RULING

The Panel noted a statement in the SPC that statistically significant improvements in pain intensity difference was seen with Effentora vs placebo as early as ten minutes in one study and as early as fifteen minutes (earliest time point measured) in another study.

The Panel noted that on the front cover of the booklet the descending scale started with 10 minutes and a 9mm vertical red line at the left hand side. Thereafter each regressive minute was marked with vertical red lines which gradually decreased in height until at zero, on the right hand side, there was no red line at all. In the Panel's view this implied that whatever was present at 10 minutes was completely gone at zero. Given its inclusion in a promotional piece about Effentora, the Panel considered that some readers would assume that the sliding scale meant that Effentora produced complete pain relief in 10 minutes which was not so. The graphic was superimposed over a

visual of a couple looking relaxed and happy. The Panel considered that the descending scale gave a misleading impression about the efficacy of Effentora as alleged. A breach of Clause 7.8 was ruled.

3 Cephalon company logo with strapline 'deliver more'

The company logo and strapline appeared in the lower left hand corner of the front cover of the booklet. The product logo was in the lower right hand corner.

COMPLAINT

ProStrakan stated that the company logo was adjacent to the product logo and on the front cover of an Effentora promotional item. The 'deliver more' text was therefore a hanging comparison in breach of Clause 7.2 of the Code.

RESPONSE

Cephalon submitted that the corporate logo/statement and Effentora logo were not within sufficient proximity of each other to be considered adjacent. This alone clearly suggested that the allegation that 'deliver more' constituted a hanging comparison in relation to Effentora was unfounded and so there was no breach of Clause 7.2. Furthermore, the statement 'deliver more' was a corporate claim, and as such was not associated with the promotion of a specific medicine. It therefore fell outside the scope of the Code.

Cephalon stated that it was unfortunate that ProStrakan had complained on this point. Cephalon had responded through inter-company correspondence that an internal decision had already been made to phase out the use of this corporate claim for other reasons.

PANEL RULING

The Director noted that in inter-company dialogue Cephalon had agreed to phase out the use of the strapline 'deliver more'; the company had not agreed to stop using it with immediate effect. Inter-company dialogue had thus been unsuccessful and so the complaint on this point could proceed.

The Panel noted Cephalon's contention that the strapline 'deliver more' was a corporate claim and thus not subject to the Code. The Panel considered, however, that in a promotional piece for a medicine a corporate strapline might be regarded as a promotional claim for that medicine. Each case would have to be judged on its own merits. In this instance the Panel considered that the corporate logo was sufficiently separated from the product logo such that 'deliver more' would not be regarded as a claim for Effentora. No breach of Clause 7.2 was ruled.

4 Images of tablet placement

For each titration dose (100mcg/200mcg/400mcg/600mcg and 800mcg) the booklet featured diagrams of a patient's face with tablets superimposed around the jaw line.

COMPLAINT

ProStrakan noted that the graphics indicated the required positioning of tablets for all doses. The images for the 600mcg (3x200mcg tablets) and 800mcg (4x200mcg tablets) doses clearly showed some tablets in the upper part of the mouth and some in the lower part of the mouth (particularly the 3x200mcg image). The Effentora SPC stated that tablets should be placed in the upper part of the buccal cavity. Thus, the information in the dose titration guide was inconsistent with the particulars in the SPC, in breach of Clause 3.2 of the Code. ProStrakan was concerned that this discrepancy might pose a safety hazard for patients.

RESPONSE

Cephalon submitted that following ProStrakan's original inter-company complaint, it had reviewed the images at issue and considered that they could be misconstrued as representing placement of Effentora in both the upper and lower portions of the buccal cavity. However, adverse events were typical of opioids and there was no evidence from safety monitoring that such placement was occurring and was associated with additional risk.

The images did not clearly show some tablets in the lower part of the mouth. The graphical representation showed that if three or four tablets were required, placement on both sides of the mouth would be necessary, and this should be two on each side. As a 2-D image, it was a challenge to demonstrate the true positioning of the buccal tablets.

In light of ProStrakan's initial inter-company complaint, Cephalon had offered to review the graphical images. Unfortunately, since the correspondence, Cephalon had already approved internally new graphical images to address this, solely in the interests of clarifying the point of buccal tablet placement rather than acceding to the alleged breach.

Therefore, Cephalon refuted the alleged breach of Clause 3.2, but considered additional clarity could be provided through re-drafting of the appropriate images.

PANEL RULING

The Director noted that in inter-company dialogue Cephalon had agreed to review the images but had not agreed to stop using them. Inter-company dialogue had thus been unsuccessful and so the complaint on this point could proceed.

The Panel considered that the images were misleading. Where more than two tablets were to be used (ie 600mcg and 800mcg doses) some of the tablets were placed on the diagram such that they appeared over the lower buccal cavity. The SPC clearly stated that tablets were to be placed in the upper portion of the buccal cavity (above an upper rear molar between the cheek and gum). The Panel considered that the images were inconsistent with the particulars listed in the Effentora SPC. A breach of Clause 3.2 was ruled.

5 Prescribing information

COMPLAINT

ProStrakan noted that the prescribing information on the inside back covers of the Titration Guidelines booklet did not list the frequency of the application site reactions. According to the SPC these were 'very common' and so this information should have been included. The frequency of other adverse events was listed, therefore this omission appeared to be trying to minimise the significance of application site reactions. A breach of Clause 4.2 was alleged.

RESPONSE

Cephalon submitted that there was no absolute requirement to state frequencies in the prescribing information. Clause 4.2 required 'a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics, together with a statement that prescribers should consult the summary of product characteristics in relation to other side effects'.

The prescribing information fulfilled these requirements. The statement relating to application site reactions stood alone for emphasis. Cephalon thus denied a breach of Clause 4.2

PANEL RULING

The Panel noted that one of the elements of prescribing information listed in Clause 4.2 was 'a succinct statement of common side-effects likely to be encountered in clinical practice'. The prescribing information at issue stated 'Application site reactions including pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles' but did not attribute any frequency to these side-effects. The Effentora SPC listed these effects as being very common. Immediately following the statement regarding application site reactions the prescribing information stated 'Very common effects (>10%) – nausea and dizziness. Common (<1%-10%) – Dysgensia, Somnolence …'. Given that frequencies of other adverse events had been stated it thus appeared that application site reactions occurred at a frequency that was something other than very common or common which was not so. To state the frequency for some adverse events but not for others was not helpful. Nonetheless the information listed in Clause 4.2 had been provided. Clause 4.2 did not require frequencies to be stated – just that common side effects be listed. Clause 4.1 required that the elements of prescribing information listed in Clause 4.2 be provided and so no breach of Clause 4.1 was ruled.

Complaint received **11 March 2009**

Case completed **6 May 2009**