CASE AUTH/2235/5/09

CEPHALON/DIRECTOR v PROSTRAKAN

Promotion of Abstral

Cephalon complained that a revised promotional campaign for Abstral (sublingual fentanyl citrate tablet) issued by ProStrakan did not accommodate the ruling of a breach of the Code with regard to a 10 minute pain relief claim (Case AUTH/2207/2/09). Not only did the campaign persist with the theme of Abstral being faster in onset than was consistent with its summary of product characteristics (SPC), it actually inferred that Abstral was even faster in onset than the 10 minutes recently ruled in breach and thus appeared to show disregard for the recent ruling.

Cephalon alleged that the advertisement heading, 'To hell and back in minutes' clearly implied that Abstral worked in a few minutes. This was further reinforced in the body of the advertisement by the claim 'Acts in minutes' referenced to the SPC. 'Acts in minutes' also appeared, unreferenced in the strapline.

As made clear in Case AUTH/2207/2/09 the SPC stated that '… Abstral has been shown to induce significantly superior pain relief from 15 minutes after administration onwards, …'. Conversely the above claims implied that it gave pain relief in a few minutes - certainly nowhere near as long as 15 minutes. Cephalon alleged that the claims were grossly misleading and inconsistent with the SPC.

Cephalon further alleged that the issue was sufficiently similar to that recently ruled in breach, such that it was not compliant with the undertaking.

As the complaint included an alleged breach of the undertaking given in Case AUTH/2207/2/09 that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The detailed response from ProStrakan is given below.

The Panel noted that Section 5.1 of the Abstral SPC (Pharmacodynamic properties) stated that '… Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards…'. Section 4.2 of the SPC (Posology and method of administration) stated that 'if adequate analgesia is not obtained within 15-30 minutes of administration of a single sublingual tablet, a second 100 microgram sublingual tablet may be administered'.

In Case AUTH/2207/2/09 the Panel noted that the claim at issue 'Rapid relief of breakthrough cancer pain from 10 minutes' was based upon data from a study but nonetheless considered that it was inconsistent with the particulars listed in the SPC and a breach of the Code was ruled.

The claims now at issue in Case AUTH/2235/5/09 were 'To hell and back in minutes' and that Abstral 'Acts in minutes'. In the Panel's view most readers would not consider 'in minutes' to be as long as the 15 minutes referred to in the SPC; some readers might even consider 'in minutes' to mean less than 10. The advertisement featured three faces of a woman showing how her expression changed as she experienced pain relief. The Panel noted that the claim in full read 'Dissolves in seconds. Acts in minutes'. In the Panel's view the depiction of only three faces and the accompanying claim 'Dissolves in seconds' added to the impression that Abstral acted very quickly. The Abstral SPC was quite specific with regard to timings whereas the advertisement left it to the reader's judgement to decide what 'in minutes' meant. This was unacceptable. Time to onset of action was particularly relevant for a medicine to treat breakthrough cancer pain; it was unhelpful not to give more details. The Panel considered ProStrakan's submission that the claim was consistent with the SPC because it used the same units of time disingenuous. The Panel considered that by not giving more information as to the time that Abstral took to act, the claims 'Acts in minutes' and 'To hell and back in minutes' were misleading and a breach of the Code was ruled. The Panel also considered that each unqualified claim was inconsistent with the particulars listed in the SPC in that most readers would assume that Abstral took less than 15 minutes to act. A breach of the Code was ruled.

The Panel noted that the claim in Case AUTH/2207/2/09, that Abstral gave relief of pain 'from 10 minutes', gave a quicker time to action for the product than stated in the SPC. It was alleged that the claim implied a statistical significance which was inconsistent with the SPC. The Panel had noted the efficacy data but considered nonetheless that the claim was inconsistent with the SPC. The Panel considered that although there were some differences between the two cases the unqualified claims now at issue, 'To hell and back in minutes' and that Abstral 'Acts in minutes', also implied a quicker time to action than stated in the SPC. The Panel further considered that the claims appeared to show a complete disregard for the previous ruling and were sufficiently similar such that they were covered by the undertaking given in that case. A breach of the Code was ruled. High standards had not been maintained; a breach of the Code was ruled.

The Panel considered that the failure to comply with the undertaking reduced confidence in, and brought discredit upon, the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

The Panel was extremely concerned that new material had been developed which might imply to some readers an even quicker time to action than the 10 minute claim previously ruled in breach of the Code. The Panel considered that the failure to comply with the undertaking together with the exacerbation of effect, warranted reporting the company to the Code of Practice Appeal Board for it to consider the matter in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted that the advertisement at issue had been used since January 2009 when Abstral was launched in the UK. The advertisement's date of preparation, March 2009, indicated when it had been re-approved following ProStrakan's review of material pursuant to the undertaking given in Case AUTH/2207/2/09. The Appeal Board was concerned that senior managers within the company had considered that the advertisement now at issue was acceptable given the outcome of the previous case.

The Appeal Board noted that ProStrakan had instigated a major review of its compliance policies and procedures (due to be completed by December 2009) and the company's submission that it had strengthened its approval system with the addition of experienced consultants which would be ongoing.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of ProStrakan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in six months' time when ProStrakan's compliance review would be complete. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the audit report the Appeal Board noted that although ProStrakan had improved its processes, procedures and skills there were, nonetheless, still some areas which needed further attention. The Appeal Board decided that ProStrakan should be reaudited. On receipt of the reaudit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the reaudit report the Appeal Board considered that progress had been made since the previous audit in January 2010. The company had plans to ensure maintenance or further improvement of standards. The Appeal Board decided that no further action was required.

Following the adverse rulings in Case Auth/2207/2/09, Cephalon complained about an Abstral (sublingual fentanyl citrate tablet) advertising campaign, issued by ProStrakan.

As the complaint included an alleged breach of the undertaking given in Case AUTH/2207/2/09 that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. ProStrakan was accordingly asked to comment in relation to Clauses 2 and 9.1 of the Code in addition to the clauses cited by Cephalon.

COMPLAINT

Cephalon complained about a revised campaign, purporting to accommodate the recent ruling relating to a 10 minute pain relief claim for Abstral (Case AUTH/2207/2/09). However, not only did it persist with the theme of Abstral being faster in onset than was consistent with the Abstral summary of product characteristics (SPC), it inferred that it was even faster in onset than the 10 minutes recently ruled in breach. As such, it appeared to show disregard for the recent ruling.

Cephalon alleged that the Abstral advertisement placed in the BMJ of 18 April 2009 (ref MO17/0134; Date of preparation: March 2009) clearly implied that Abstral worked in a few minutes by the heading which prominently stated 'To hell and back in minutes', further reinforced in the body of the advertisement by the claim 'Acts in minutes' referenced to the SPC. The wording 'Acts in minutes' also appeared, unreferenced in the strapline.

As made clear in Case AUTH/2207/2/09 the SPC (Section 5.1 Pharmacodynamic properties) stated that '… Abstral has been shown to induce significantly superior pain relief from 15 minutes after administration onwards, …'. This was in sharp contrast to the above claims which implied that it gave pain relief in a few minutes. To clinicians, 'in minutes' would without doubt imply a rapid speed of onset of pain relief, namely a few minutes - certainly nowhere near as long as 15 minutes. Cephalon alleged that the claims were grossly misleading and inconsistent with the Abstral SPC, in breach of Clauses 7.2 and 3.2.

Cephalon requested that the advertisement, and any other items making similar claims in the current campaign, be reviewed with regard to its concerns outlined above, in particular bearing in mind the recent ruling that a 10 minute claim for pain relief was ruled in breach of Clause 3.2.

Cephalon alleged that the breaches outlined above persisted in giving the seriously misleading impression that the speed of onset of pain relief was considerably faster than the 10 minutes recently ruled in breach for being inconsistent with the 15 minutes stated in the Abstral SPC. Cephalon further alleged that the issue was sufficiently similar

to that recently ruled in breach, such that it was not compliant with the undertaking in breach of Clause 25.

RESPONSE

ProStrakan denied that the claims at issue were in breach of Clauses 7.2 and 3.2 of the Code. The claims 'To hell and back in minutes' and 'Acts in minutes' were accurate, fair and unambiguous descriptions of the onset of effect of Abstral and were not inconsistent with the SPC.

ProStrakan submitted that Section 5.1 of the Abstral SPC stated that the product had shown 'significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards'. The claim 'Acts in minutes' was therefore consistent with the SPC which used minutes as the unit of time to describe the onset of effect. It would have been misleading to represent the onset of effect in terms of a smaller unit of time (seconds) but the SPC described efficacy as being seen in terms of minutes. Breakthrough cancer pain was a 'transitory' or 'transient' exacerbation of pain. Abstral was specifically licensed to treat this type of rapid onset, short-lived pain. Therefore the claim 'To hell and back in minutes' was an accurate representation of the course of an episode of breakthrough cancer pain which was treated with Abstral, and was also consistent with the SPC.

ProStrakan submitted that this perspective was supported by official guidance and expert opinion. Cephalon objected to claims that Abstral had onset of effect 'in minutes' on the grounds that this suggested a rapid speed of onset of pain relief. In fact this was appropriate. Guidance from the Medicines and Healthcare product Regulatory Agency (MHRA) on the use of 'fast-acting' claims stated that onset of effect of 30 minutes would be required to support a claim of 'fast-acting' for products such as those for acute pain relief or hayfever treatments. Abstral's onset of effect was well within this time period and so the product could be regarded as fast-acting. Recommendations on management of breakthrough cancer pain stated that treatment should have a rapid onset of effect seen 'within minutes' (Bennett *et al* 1998, Coluzzi *et al* 1998).

Clinicians had historically used immediate release oral opioids in the management of breakthrough cancer pain and they continued to be the mainstay of treatment; their onset of effect was 20-30 minutes (Davies *et al* 2009). Given that Abstral worked from 15 minutes it seemed reasonable to describe it in terms that were consistent with a faster onset of action than standard treatment.

ProStrakan was very concerned about the allegation of a breach of the undertaking given in Case AUTH/2207/2/09. ProStrakan took compliance with the Code extremely seriously and quickly sought guidance from the PMCPA when the accusation of a breach of undertaking was first made by Cephalon. In line with the undertaking, ProStrakan discontinued use of all materials containing the claim ruled in breach or similar claims with effect from 13 March 2009. All sales and marketing materials containing the claim at issue or similar claims were withdrawn. When developing new materials ProStrakan was anxious to ensure that it described the onset of effect of Abstral, which was an important feature in the management of breakthrough pain, in a manner which was both helpful to prescribers and consistent with the SPC. ProStrakan submitted that its current campaign respected its undertaking and was therefore not in breach of Clause 25. Through its actions, which had been prompt and thorough, it had maintained high standards and had not brought discredit on the industry; ProStrakan did not believe that it had breached Clauses 9.1 or 2 of the Code.

PANEL RULING

The Panel noted that Section 5.1 of the Abstral SPC (Pharmacodynamic properties) stated that '…Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards…'. Section 4.2 of the SPC (Posology and method of administration) stated that 'if adequate analgesia is not obtained within 15-30 minutes of administration of a single sublingual tablet, a second 100 microgram sublingual tablet may be administered'.

In the previous case, Case AUTH/2207/2/09, the Panel noted that the claim at issue 'Rapid relief of breakthrough cancer pain from 10 minutes' was based upon the efficacy data from study EN3267-005. Nonetheless the Panel considered that the ten minute claim was inconsistent with the particulars listed in the Abstral SPC and a breach of Clause 3.2 of the Code was ruled.

The claims now at issue in Case AUTH/2235/5/09 were 'To hell and back in minutes' and that Abstral 'Acts in minutes'. In the Panel's view most readers would not consider 'in minutes' to be as long as the 15 minutes referred to at Section 5.1 of the SPC; some readers might even consider 'in minutes' to mean less than 10. The advertisement featured three faces of a women showing how her expression changed as she experienced pain relief. The Panel also noted that 'Acts in minutes' was preceded by 'Dissolves in seconds' so the claim in full read 'Dissolves in seconds. Acts in minutes'. In the Panel's view the depiction of only three faces and the accompanying claim 'Dissolves in seconds' added to the impression that Abstral acted very quickly. The Abstral SPC was quite specific with regard to timings whereas the advertisement left it to the reader's judgement to decide what 'in minutes' meant. This was unacceptable. Time to onset of action was particularly relevant for a medicine to treat breakthrough cancer pain; it was unhelpful not to give more details. The Panel

considered ProStrakan's submission that the claim was consistent with the SPC because it used the same units of time disingenuous. The Panel considered that by not giving more information as to the time that Abstral took to act, the claims 'Acts in minutes' and 'To hell and back in minutes' were misleading and a breach of Clause 7.2 was ruled. The Panel also considered that each unqualified claim was inconsistent with the particulars listed in the SPC in that most readers would assume that Abstral took less than 15 minutes to act. A breach of Clause 3.2 was ruled.

The Panel noted that whilst the material in question was different to that considered in Case AUTH/2207/2/09, the issue was whether it was caught by the undertaking previously given. The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the claim in Case AUTH/2207/2/09, that Abstral gave relief of pain 'from 10 minutes', gave a quicker time to action for the product than stated in the SPC. It was alleged that the claim implied a statistical significance which was inconsistent with the SPC. The Panel had noted the efficacy data but considered nonetheless that the claim was inconsistent with the SPC. The Panel considered that although there were some differences between the two cases the unqualified claims now at issue, 'To hell and back in minutes' and that Abstral 'Acts in minutes', also implied a quicker time to action than stated in the SPC. The Panel further considered that the claims appeared to show a complete disregard for the previous ruling and were sufficiently similar such that they were covered by the undertaking given in that case. A breach of Clause 25 was ruled. High standards had not been maintained; a breach of Clause 9.1 was ruled.

The Panel considered that the failure to comply with the undertaking reduced confidence in and brought discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was extremely concerned that new material had been developed which might imply to some readers an even quicker time to action than the 10 minute claim previously ruled in breach of the Code. The Panel considered that the failure to comply with the undertaking together with the exacerbation of effect, warranted reporting the company to the Code of Practice Appeal Board for it to consider the matter in accordance with Paragraph 8.2 of the Constitution and Procedure.

During the consideration of this case the Panel noted ProStrakan's submission regarding the MHRA's guidance on the use of 'fast-acting' claims. The MHRA noted that claims for fast relief of symptoms would be relevant for products for acute pain relief and hay fever. A rule of thumb for hay fever products would require onset of relief within about 30 minutes to support a 'fast-acting' claim. No time to onset of relief was stated for analgesics. The Panel was concerned that ProStrakan had misrepresented the MHRA guidance in this regard and requested that the company be so advised.

PROSTRAKAN'S COMMENTS ON THE REPORT

ProStrakan regretted the breach of the Code to which the current case related. Data from a new study showing onset of effect in ten minutes for Abstral had been included in the European promotional campaign and had been successfully defended in at least one other EU country. A UK advertisement containing this claim was derived from the European materials. This advertisement was reviewed, approved and certified through ProStrakan's copy approval system. As ProStrakan had acknowledged, the claim of ten minute onset was inconsistent with the fifteen minutes specified in the pharmacodynamics section of the SPC, in breach of Clause 3.2 (Case AUTH/2207/2/09).

When ProStrakan received the outcome of Case AUTH/2207/2/09 it was reviewed by senior management and the approval team. Once ProStrakan understood the nature of the error it was clear that it had no grounds for appeal and the approval team immediately identified, withdrew and reissued all materials containing the ten minute claim. This was a demanding piece of work for a small team in order to complete all activities within the five day time period required in the undertaking.

ProStrakan explained that in developing new materials the team considered a number of alternative options to describe Abstral's speed of onset. Breakthrough cancer pain was an area where prompt onset of pain relief was particularly important to patients. Prescribers needed to understand the profile of the various options for cancer pain management in order to match the appropriate medicine and formulation to the correct indication. Abstral materials had previously used the claims 'To hell and back in minutes' and 'Acts in minutes' and the approval team considered that these claims were a good representation of the profile of the product and were approvable for use in the UK. They specifically considered the important issue of whether these claims were in breach of the undertaking already given and concluded (on the basis of the arguments given in ProStrakan's response to the Panel) that they were not. As a result these claims were not removed from the original materials. This was a very serious error of judgement which had resulted in significant financial costs to the company from withdrawing and revising material again and, more importantly, a potential loss of reputation.

ProStrakan understood why the Panel considered

that the argument used to support the claims was disingenuous. However, the approval team had concluded that 'in minutes' was a true reflection of the onset of effect and it would not be understood by target customers to mean less than fifteen minutes. This genuinely held perspective was not morally fraudulent but it was naïve. The group had clearly failed to consider the effect of the advertisement as a whole or the risk that not only might readers consider 'in minutes' to mean something less than fifteen minutes, but that they might also consider it to mean less than ten minutes.

ProStrakan submitted that when it received the complaint from Cephalon the approval team sought advice from the Authority on the complaint and the procedure for seeking conciliation. The offer of conciliation was driven by a conviction that the claims and arguments were sound and that an independent third party would come to the same conclusion. To many people this view might be difficult to comprehend. In the Panel's view most readers would understand 'in minutes' as meaning something less than fifteen minutes; in this respect the approval team appeared to have represented a minority of readers (the target audience of prescribers for breakthrough cancer pain), but it failed to recognise this. As atypical readers coming to the piece with pre-conceived ideas their views were not necessarily those of a customer.

ProStrakan submitted that very regrettably, the outcome of this unchallenged 'group think' approach was an advertisement in the BMJ which suggested to some readers that Abstral had an onset of effect of less than 10 minutes and appeared to indicate a complete disregard for the previous ruling, as the Panel had described. However, the approval team had confirmed that it believed that it had taken the previous ruling carefully into account when devising the new claims; no-one had seen the potential for some readers to understand 'in minutes' as 'a few minutes'. In reality this was not 'complete disregard'; the team understood that the undertaking was a serious matter and it believed it had considered it, but its thinking was blinkered, self-censored and fell a long way short of the required rigour.

The Panel's concerns about the company's approach to the regulations appeared to have been compounded by its concern that ProStrakan had misrepresented the MHRA's advice about fast-acting claims. This was not ProStrakan's intention. The wording used was a clumsy attempt to summarise guidance which it believed was relevant to this complaint. ProStrakan acknowledged that the MHRA guidance stated that the timing was dependent on the indication and that the 30 minutes was specifically mentioned in relation to hayfever and regretted not having made this clearer.

ProStrakan submitted that this case constituted a 'critical incident' in terms of its review and approval processes and the company had reviewed it as such. Both the current and previous case arose from errors of interpretation and judgement due to inwardly focused and insufficiently rigorous thinking within an insulated and highly cohesive group. ProStrakan did not believe there was a systemic failure in its processes; all materials were carefully reviewed and certified through its electronic approval system. ProStrakan's action plan to reduce the risk of such an event happening again was as follows:

a) Once the case was published the general manager would provide details of it to all employees and reinforce the importance of a Code compliant culture throughout the company.

b) All staff and contractors involved with preparation, review and certification of UK and European materials would undergo Code refresher training by 1 October 2009.

c) Sales and marketing teams would be informed about relevant published Code cases with regular review at monthly team meeting.

d) Roles and responsibilities within approval teams would be changed to promote critical evaluation, specifically:

- Development of an 'Approval team charter' to encourage expression of dissenting views, thorough review of alternative approaches and formal consideration of risks of preferred choice
- External consultant to review all UK materials.

e) External consultant (Code compliance expert) engaged to thoroughly review company Code culture, policies and processes.

ProStrakan submitted that these actions would promote the importance with which it regarded the Code throughout the company, improve the quality of its approval processes and reduce the risk of future breaches.

In line with the undertaking ProStrakan had critically evaluated all Abstral promotional materials and had removed any material which could imply an onset of action of less than fifteen minutes. In order to improve objectivity these materials had also been reviewed by an external consultant.

In conclusion, ProStrakan submitted that the comments above were not intended to justify or mitigate its actions and decisions; the comments represented the outcome of an internal review carried out in order to understand what went wrong and prevent reoccurrence. ProStrakan fully appreciated the severity of these matters and greatly regretted that its action had brought discredit on the industry.

APPEAL BOARD CONSIDERATION

The Appeal Board noted that the advertisement at issue had been used since January 2009 when Abstral was launched in the UK. The advertisement's date of preparation, March 2009, indicated when it had been re-approved following ProStrakan's review of material pursuant to the undertaking given in Case AUTH/2207/2/09. The Appeal Board was concerned that senior managers within the company had considered that the advertisement now at issue was acceptable given the outcome of the previous case.

The Appeal Board noted that as a result of the rulings in this case, Case AUTH/2235/5/09, ProStrakan had instigated a major review of its compliance policies and procedures which was due to be completed by December 2009. The Appeal Board noted ProStrakan's submission that it had strengthened its approval system with the addition of experienced consultants and this would be ongoing.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of ProStrakan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in six months' time when ProStrakan's compliance review would be complete. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

In accordance with Paragraph 13.6 of the Constitution and Procedure the Appeal Board decided that an interim case report should be published on the PMCPA website.

APPEAL BOARD FURTHER CONSIDERATION

The audit was conducted in January 2010. The Appeal Board noted that although ProStrakan had improved its processes, procedures and skills there were, nonetheless, still some areas which needed further attention. The Appeal Board decided that ProStrakan should be reaudited. On receipt of the reaudit report the Appeal Board would consider whether further sanctions were necessary.

The reaudit was conducted in July 2010. The Appeal Board considered that progress had been made since the previous audit. The company had plans to ensure maintenance or further improvement of standards. The Appeal Board decided that no further action was required.

Complaint received	**28 May 2009**
Undertaking received	**3 July 2009**
Appeal Board Consideration	**23 July 2009, 24 February 2010, 22 July 2010**
Interim Case Report published	**26 August 2009**
Case completed	**22 July 2010**