CASE AUTH/2207/2/09

CEPHALON v PROSTRAKAN

Promotion of Abstral

Cephalon alleged that the claim 'Rapid relief of breakthrough cancer pain from 10 minutes', used by ProStrakan to promote Abstral (sublingual fentanyl citrate tablet), was inconsistent with the particulars listed in the summary of product characteristics (SPC) in breach of the Code.

The detailed response from ProStrakan is given below.

The Panel noted that Section 5.1 of the Abstral SPC (Pharmacodynamics properties) stated that '…Abstral has been shown to induce significantly superior relief of breakthrough pain compared with 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 simple sublingual tablet, a second 100 microgram sublingual tablet may be administered'.

The Panel noted that the claim for 'Rapid relief of breakthrough cancer pain from 10 minutes' was based upon efficacy data from a study. Nonetheless the ten minute claim was inconsistent with the Abstral SPC and the Panel thus ruled a breach of the Code.

Cephalon (UK) Limited complained about the promotion of Abstral (sublingual fentanyl citrate tablet) by ProStrakan Ltd. The materials at issue were two leavepieces (refs MO17/0070 and MO17/0101). Inter-company dialogue had failed to resolve the issues.

Claim 'Rapid relief of breakthrough cancer pain from 10 minutes'

This claim was referenced to data on file – Study EN3267-005 in both leavepieces.

COMPLAINT

Cephalon alleged that the claim was inconsistent with the marketing authorization. Section 5.1 of the Abstral summary of product characteristics (SPC) stated:

> 'In patients with chronic pain on stable maintenance doses of opioids, Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards, …'.

Thus the claim for relief from 10 minutes implied statistical significance which was inconsistent with the particulars listed in the SPC in breach of Clause 3.2 of the Code.

RESPONSE

ProStrakan stated that the licensed indication for Abstral was 'Management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain'. ProStrakan also stated that breakthrough cancer pain, a transitory exacerbation of pain that occurred on a background of otherwise stable pain (Portenoy and Hagen 1990) was a common condition in cancer patients (Patt 1998). Breakthrough cancer pain was characterised by a rapid onset and short duration, often reaching peak intensity in as little as 3 minutes and lasting, on average, 30 minutes (Bennett *et al* 2005, Simmonds 1999). The maximum intensity of breakthrough cancer pain was often moderate to severe (Skinner *et al* 2006). It had a significant impact on patients' quality of life, including effects on patient activity, relationships and mood (Caraceni *et al* 2004, Portenoy and Hagen) and caused increased treatment costs (Fortner *et al* 2002).

Conventional treatment strategies for cancer pain comprised 24 hour analgesia to control background pain, with additional analgesics, such as immediate-release morphine, provided as needed to control episodes of breakthrough cancer pain (Bennett *et al*). However, many commonly used analgesics did not display a time-action profile suitable to match the rapid-onset, short-lived nature of breakthrough cancer pain (Bennett *et al*). The successful treatment of breakthrough cancer pain required fast-acting, potent analgesics; time to onset of analgesia was of key importance. ProStrakan was therefore committed to providing health professionals with the most recent and appropriate information about the efficacy of Abstral, and in particular onset of effect.

The potency and rapid absorption of oral transmucosal fentanyl products made them ideal for the treatment of breakthrough cancer pain but also conferred considerable clinical risk when used inappropriately. A recent US safety alert for Fentora (fentanyl buccal tablets) highlighted the serious and sometimes fatal consequences of inappropriate or inaccurate prescribing and use of these products. ProStrakan considered that the safety of patients using transmucosal fentanyl products such as Abstral was best served by providing prescribers with the most up-to-date information.

ProStrakan stated the information in Section 5.1 of the current Abstral SPC was derived from a Phase II

study, SuF 002; this was a Swedish-based, randomised, multicentre, double-blind, four-period crossover study conducted in opioid-tolerant male and female Caucasian patients with locally advanced or generalised cancer and breakthrough cancer pain (Lennernäs *et al* 2008). Patients took single doses of 100, 200 and 400mcg Abstral and placebo in a random order and without any dose titration. Twenty-three patients completed all four treatment periods; 15 did not complete the study according to protocol. The intent-to-treat (ITT) population comprised 27 patients, while 23 patients formed the per-protocol set (PPS). In the PPS, the shape of the time curve for mean pain intensity difference showed a significant overall improvement in pain intensity over the whole treatment period with Abstral 400mcg compared with placebo (8.57mm, p<0.001), with visual separation of the curves being seen as early as 5 minutes post-dose. These findings were replicated in the ITT population.

ProStrakan stated that improvement in pain intensity was greater with Abstral 400mcg compared with placebo, with this effect being evident at all time points assessed and becoming statistically significant from 15 minutes onwards post-dose (p=0.005).

ProStrakan stated that study EN3267-005 was a double-blind, randomised, placebo-controlled, multicentre study to evaluate the efficacy and safety of Abstral for the treatment of breakthrough pain in opioid-tolerant cancer patients followed by an up to 12-month non-randomised, open-label extension to assess long-term safety. In this study patients started the titration phase with 100mcg Abstral. If this dose was inadequate they moved to the next highest dose strength for the subsequent episode of breakthrough pain. This process continued through the available dose strengths of 100, 200, 300, 400, 600 and 800mcg until a patient identified a single effective Abstral dose that treated all episodes of breakthrough pain on 2 consecutive days. Following successful titration the patients were randomised to the double-blind phase where 10 doses of study medication were provided comprising 7 doses of Abstral (at the stable dose determined in the titration phase for that patient) and 3 matching placebo doses. Ninety-seven percent of the patients that completed the titration phase and entered the randomisation phase then elected to continue into the open label phase of the study where they continued to receive Abstral to treat breakthrough cancer pain for up to 12 months and safety data only was collected. The primary objective of the study was to compare the efficacy of Abstral with that of placebo as measured by the sum of pain intensity difference from baseline to 30 minutes after dosing. Secondary objectives included assessment of pain intensity difference, pain relief and rescue medication use.

ProStrakan stated that the efficacy phase data was analysed in December 2007 (study EN3267-005 data on file). The analysis of data from the ITT population (n=61) and the PP set (n=45) demonstrated that Abstral was superior to placebo in treating cancer breakthrough pain as measured by sum of pain intensity difference during a breakthrough episode.

ProStrakan stated that Abstral was shown to provide improved reduction in pain intensity from the first measured time point (10 minutes) that was significantly different to placebo (1.16 vs 0.88 respectively; p=0.0055). This statistically significant difference was also present at 15 minutes and was maintained to 60 minutes.

Following a comprehensive review of the EN3267-005 efficacy data, ProStrakan was confident in its robustness and validity and had made them available to UK health professionals caring for patients with breakthrough cancer pain. In December 2008 an abstract of the data was accepted for presentation at the World Institute of Pain meeting in March 2009 in New York (Rauck *et al* 2009). ProStrakan noted that this abstract referred to 'interim' results for this study. The efficacy data presented above and in the abstract were not interim. It was the safety data that was interim as the final safety dataset had not been fully analysed when the abstract was submitted.

Comparison of Phase II and Phase III studies and Abstral SPC

ProStrakan highlighted the key differences between the Phase II and Phase III studies and compared these with the current SPC for Abstral (table below). As this table showed, the Phase III study used the same starting dose, dose titration scheme and dose range as the current UK SPC for Abstral, in contrast to the Phase II study. Additionally, the Phase III study used a larger sample size and measured pain intensity in more than 5 times as many pain episodes than the Phase II study

	Phase II study	**Phase III study**	**Abstral SPC**
Sample size	27 patients	61 patients	
Number of pain episodes assessed per patient	1 per dose (4 total)	10	
Total pain episodes assessed	108	561	
Starting dose	100-400mcg	100mcg	100mcg
Dose range	100-400mcg	100-800mcg	100-800mcg
Ascending titration through available dose strengths (100, 200, 300, 400, 600 and 800mcg)	No	Yes	Yes

ProStrakan stated that the following data was derived from the EN3267-005 Phase III study and a further Phase III long-term safety study (EN3267-007) that used the same titration method as study 005 (study EN3267-005 and study EN3267-007 data on file). The Abstract Phase III dose data demonstrated that the full range of Abstral doses

was required to successfully treat breakthrough cancer pain. Of particular significance was that 48% of patients required final Abstral doses of either 600 or 800mcg (doses that were not used in the Phase II study). These results further indicated the importance of the Phase III data where all doses were assessed.

ProStrakan noted that the current SPC stated 'Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards' was based on data from the Phase II study. The EN3267-005 Phase III study also demonstrated pain relief at 15 minutes, therefore it did not contradict what was shown in the Phase II study, nor the current SPC. Additionally, the Phase III study showed that Abstral, when used correctly under the conditions specified in the current SPC (particularly starting at 100mcg, dose titrating and utilising the entire dose range of 100-800mcg where necessary), could result in significant pain relief from as early as 10 minutes. ProStrakan therefore considered it appropriate to make this information available to health professionals who were using Abstral as directed by the SPC.

ProStrakan stated that the Phase III data and the 10 minute claim were also plainly referenced in all materials as coming from the EN3267-005 study and were therefore clearly distinct from the data contained in the SPC.

ProStrakan noted that Clause 7.2 of the Code required all claims to be based on 'an up-to-date evaluation of all the evidence and reflect that evidence clearly'. By considering the Phase III data when formulating claims, ProStrakan believed it had acted in line with this requirement. Furthermore, the European Medicines Evaluation Agency's guideline on SPCs stated that in Section 5.1 'It may be appropriate to provide limited information, relevant to the prescriber…regarding pre-specified end points or clinical outcomes'. This section of the SPC was therefore not intended to be a definitive summary of all the efficacy data pertaining to a particular medicine.

In conclusion, ProStrakan denied a breach of Clause 3.2. As detailed above, the Phase III data was collected under conditions that were much more consistent with the dosage and administration stated in the current SPC than the Phase II study. The Phase III data also demonstrated efficacy at 15 minutes and was consequently not inconsistent with the current SPC. The Phase III data was therefore up-to-date, relevant and robust. As such, it was of central importance for health professionals treating breakthrough cancer pain. ProStrakan had therefore published this data and included it in its promotional materials in order to enhance the care of patients with this debilitating condition. ProStrakan firmly believed that, for the reasons outlined above, such behaviour did not contravene either the letter or the spirit 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 with 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 simple sublingual tablet, a second 100 microgram sublingual tablet may be administered'.

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 ten minute claim was inconsistent with the particulars listed in the Abstral SPC and the Panel thus ruled a breach of Clause 3.2 of the Code.

Complaint received **11 February 2009**

Case completed **16 March 2009**