ANONYMOUS v PROSTRAKAN

Promotion of Abstral

An anonymous non-contactable complainant who worked in a specialist burns unit alleged that a medical liaison specialist from ProStrakan had promoted the off-label use of Abstral (fentanyl) sub-lingual tablets. Abstral was indicated for the management of breakthrough pain in adults who used opioids for chronic cancer pain.

The complainant explained that he/she had recently been visited by a ProStrakan employee whom he/she agreed to see only because the employee claimed to be an medical liaison specialist (not a sales representative). The complainant stated that he/she was surprised when the company representative did not show any off label data at all; the only data the complainant was shown related to studies in breakthrough cancer pain when patients were otherwise controlled on a background of around the clock sustained release morphine or equivalent.

The complainant stated that the medical liaison specialist continued to question him/her and it soon became clear that the medical liaison specialist was interested in the complainant's prescribing of fentanyl lozenges [Actiq marketed by Cephalon]. The speed of action of the two medicines was compared relating this to dressing changes or movement. The complainant asked for supporting data but none was forthcoming. The complainant assumed that there was no data in this cohort of patients.

If companies discussed off-licence use they should at least have some off-licence data. As far as the complainant could establish, the medical liaison specialist had no medical training and no off-licence data. The complainant considered that the medical liaison specialist's conduct was a flagrant attempt to widen the prescribing of Abstral.

The detailed response from ProStrakan is given below.

The Panel noted that the complainant was anonymous and non contactable and that, as set out in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and, like all complaints, judged on the evidence provided by the parties. The complainant had submitted no material to support his/her position. The Panel also noted the difficulty of dealing with complaints based on one party's word against the other.

The Panel considered that companies had to be extremely careful in ensuring that their medicines were not promoted for unlicensed indications. The role of MLE staff and the like needed to be very carefully controlled with detailed instructions. Guidance in this regard had recently been published in the PMCPA guidance on Clause 3 of the Code.

The Code defined a representative as anyone calling on members of the health professions and administrative staff in relation to the promotion of medicines. This was a wide definition and could cover the activities of those employees that companies might not call representatives. The Code defined 'promotion' as 'any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines'.

The Panel noted that the parties' accounts differed. The complainant stated that he/she had agreed to see a medical liaison executive (MLE) who showed him/her data relating to studies in breakthrough cancer pain and was interested in his/her prescribing of a competitor medicine in the specialist burns unit. The MLE compared the two medicines in relation to speed of action and related this to dressing changes and movement. The complainant alleged that the MLE had no data to support the use of Abstral in this cohort of patients. ProStrakan had submitted that its procedures only permitted MLEs to interact with burns units following an unsolicited request for information from that individual. Proactive, routine and unsolicited discussion of the off-label use of Abstral was prohibited by ProStrakan. ProStrakan had also submitted that the MLE team did not discuss both licensed and unlicensed use of Abstral in the same call. If a health professional asked an unsolicited question about the licensed use of Abstral during a discussion of off-licence use the MLE would answer that question.

The Panel further noted ProStrakan's submission that between February 2011 and May 2012 its MLE team had received only three requests relating to the use of Abstral in burns patients. In all cases these interactions had been prompted by requests for information by the health professional.

The Panel noted ProStrakan's submission that its MLE team was a field based extension of its medical information function. On reviewing the MLE job description, the Panel noted the role was split into two, a reactive part (referred to in ProStrakan's response) and a proactive part which was made up of two functions; firstly to engage with stakeholders regarding within licence scientific data in a balanced, non-promotional way and secondly to proactively contact external stakeholders in relation to scientific publication, clinical studies, disease awareness and non promotional new data. To this extent, the Panel considered that this role went beyond that of a medical information department. The Panel further

noted the informal guidance on Clause 3 of the Code issued by the Authority.

The Panel thus considered that one aspect of the MLE role as described in the job description was likely to involve the promotion of ProStrakan medicines. In the Panel's view the job description meant that MLEs would call proactively on health professionals and this may have included the call upon the complainant. ProStrakan had not commented on the discussion regarding fentanyl lozenges.

The Panel considered that the parties' accounts differed and it was not possible to determine where the truth lay. On the very limited information provided by the complainant it was not possible for ProStrakan to identify the MLE/representative involved. It was not possible to contact the complainant for more information. The Panel considered that the complainant had not established his/her case on the balance of probabilities. No breach of the Code was ruled including no breach of Clause 2.

An anonymous non-contactable complainant alleged that a medical liaison specialist from ProStrakan had promoted the off-label use of Abstral (fentanyl) sub-lingual tablets. Abstral was indicated for the management of breakthrough pain in adults who used opioids for chronic cancer pain.

COMPLAINT

The complainant explained that he/she had recently been visited by a ProStrakan employee whom he/she agreed to see only because the employee claimed to be an medical liaison specialist (not a sales representative). The complainant explained that he/she worked in a specialist burns unit and needed a portfolio of pain medicines.

The complainant stated that he/she was surprised when the company representative did not show any off label data at all; the only data the complainant was shown related to studies in breakthrough cancer pain when patients were otherwise controlled on a background of around the clock sustained release morphine or equivalent.

The complainant stated that the medical liaison specialist continued to question him/her and it soon became clear that the medical liaison specialist was interested in the complainant's prescribing of fentanyl lozenges [Actiq marketed by Cephalon]. The speed of action of the two medicines was compared relating this to dressing changes or movement. The complainant asked for supporting data but none was forthcoming. The complainant could only assume that there was no data in this cohort of patients.

The complainant understood that if companies discussed off-licence use they should at least have some off-licence data. As far as the complainant could establish, the medical liaison specialist had no medical training and no off-licence data. The complainant considered that the medical liaison specialist's conduct was a flagrant attempt to widen the prescribing of Abstral.

The complainant questioned the medical liaison specialist as to the validity of his/her conduct and was told that it was endorsed by the company from senior management down and that it was perfectly legitimate. The complainant was also told that a significant UK team had daily discussions as above.

The complainant alleged that use of fentanyl products without the appropriate expertise and knowledge was dangerous, and lethal in the wrong environment. This practice concerned the complainant greatly.

When writing to ProStrakan the Authority asked it to respond in relation to the requirements of Clauses 2, 3.1, 9.1, 15.2 and 15.9.

RESPONSE

ProStrakan explained that its field-based team of medical liaison specialists, called medical liaison executives (MLEs), reactively responded to questions from health professionals about the off-label use of Abstral. The team was an extension of the medical information function and as such reported exclusively to the medical director (latterly to the senior vice president for Northern Europe as the post of medical director was vacant). The MLE team was established to provide balanced, non-promotional, scientific and technical support to those health professionals who requested it.

ProStrakan submitted that MLE activity was wholly separate to that of the promotional sales teams. If a sales representative was asked about the off-label use of ProStrakan's products he or she might pass this on to the MLE team, but responses to such questions must be completed and delivered by the MLE team through appropriate and separate non-promotional channels.

ProStrakan explained that its procedures only permitted MLEs to interact with health professionals in burns units if they had an unsolicited request for information from that individual. Proactive, routine and unsolicited discussion of the off-label use of Abstral was strictly prohibited as this would violate the Code.

ProStrakan noted the allegation that the complainant was proactively contacted by a company employee to discuss the off-label use of Abstral. This was a serious allegation and as such ProStrakan hoped to be able to investigate the matter further but the lack of detail from the anonymous complainant and the fact that the complainant could not be contacted for further information, meant that it was difficult to fully investigate the complaint. Furthermore, there was no hint at the geographical location of the complainant that would help to focus any further investigations.

ProStrakan submitted that its investigations showed that between February 2011 and May 2012 the MLE team received 432 requests to respond to health

professionals about the use of its products. Of these, three requests were about the use of Abstral in burns patients and all had been prompted by requests from the health professional for information as described above.

ProStrakan was assessing an investigator sponsored trial (IST) proposal submitted by a physician who worked in a burns unit. This proposal, which included off-label use of Abstral, was first discussed with an MLE who helped the individual in question to prepare the application now being considered by the ProStrakan IST committee. ProStrakan reiterated that this study proposal was initiated by the health professional concerned.

ProStrakan had not sought to extend the marketing authorization for Abstral to include burns patients.

ProStrakan submitted that the MLEs did not discuss both the licensed and unlicensed use of Abstral in the same call. The MLE team had been trained to respond only to the specific question asked by a health professional with regard to off-label use, so as not to provide any further detail on topics not mentioned in the original request and that might be construed as promotional.

ProStrakan noted that its MLEs had been interviewed and asked if they discussed both licensed and unlicensed use of Abstral in the same call. Their responses reflected the training that they received. However, it was noted that customers had, on occasion, asked for the licensed indications of Abstral to be clarified while they discussed the original off-label question. In such instances the MLE would provide the information sought, but only after they had reiterated the non-promotional nature of their role to the health professional concerned.

ProStrakan noted that no training materials, briefing documents or any other items had been produced for the MLE team that discussed the use of Abstral in burns patients.

In conclusion, given their status as an extension of the medical department, and the fact that their activity with regard to the discussion of off-label product use was reactive only, ProStrakan maintained that its MLE function was as a field-based, non-promotional medical information service, an activity which was entirely distinct and different to that provided by the sales team. While MLEs engaged in off-label discussions with health professionals, these discussions were entirely at the request of the health professionals in question and maintained a high standard of ethical conduct that complied with all relevant requirements of the Code. As such ProStrakan did not believe that Clauses 3.2 or 15.2 had been breached. As there were no MLE materials of any description that discussed or advocated the use of Abstral in burns patients, either directly or indirectly, ProStrakan did not consider that Clause 15.9 had been breached.

ProStrakan stated that its MLE team was established to provide a scientific service to the medical community and that it had appropriate training and procedures to ensure that the service was provided in an ethical and compliant fashion. The company therefore submitted that high standards had been upheld; no breach of Clause 9.1 had occurred and consequently a ruling of a breach of Clause 2 was not justified.

ProStrakan submitted that although it respected the anonymity of the complainant, that anonymity not only limited the company's ability to investigate the allegations in more detail, but it also deprived the company of the standard reassurances provided by the PMCPA that the complainant had been asked to declare any conflict of interest. In that regard ProStrakan noted that one of its MLEs had recently been dismissed, although not for issues relating to performance or compliance.

Following a request for further information, ProStrakan submitted that the MLEs were expected to proactively stay abreast of developments in the scientific field in which they were working. It was anticipated that they would be aware of new data and publications in the relevant therapy area, including disease-specific and therapy-specific publications and guidelines, and that they would share this information with their colleagues in the medical department so that any information exchange and information updates could be internally coordinated.

ProStrakan stated that while the MLE job description mentioned that the team might provide 'proactive customer support' there had not yet been an occasion where such proactive contact has been necessary. If this were to occur in the future then any 'proactive customer support' would be in relation to the exchange of 'within licence' scientific data in a balanced, non-promotional manner and not in conjunction with any promotional-related person or strategy, eg to make customers aware of emergent phase IV data for Abstral within its licensed indication.

ProStrakan submitted that the MLE team was re-interviewed as a consequence of the PMCPA's request for further information. The responses given by all team members during these interviews consistently backed-up the description given above in relation to providing proactive support.

ProStrakan confirmed that MLEs did not proactively mention or discuss competitor products with health professionals. If during a call with a health professional the subject of competitors was raised by the health professional, the MLE would briefly answer any questions they were specifically asked, but point out that promotional discussions would have to be held with a sales representative from the company. They would then offer to arrange for the health professional to be contacted by the appropriate sales representative at a future date.

ProStrakan submitted that the key data relating to the onset of action of Abstral came from Rauck *et al* (2009). This was a randomised, placebo-controlled

trial in 131 opioid-tolerant patients with breakthrough cancer pain. Sixty one patients were assessed for efficacy at 10 minute intervals over a 60 minute period. Pain intensity difference (PID) was calculated by comparing pain intensity scores (rated from 0-10, where 0 is 'no pain' and 10 is 'pain as bad as you can imagine') at baseline and after treatment. Significant improvements in PID were seen from 10 minutes with Abstral vs placebo. Additionally, significant improvements in PID were maintained throughout the 60 minute assessment period. These findings were consistent with the description of the pharmacodynamic properties of Abstral in section 5.1 of the Abstral summary of product characteristics (SPC).

ProStrakan stated that the key data relating to the onset of action for Actiq came from Coluzzi *et al* (2001). This was a double-blind, double-dummy, randomised, multiple cross-over study conducted in 134 adult ambulatory cancer patients. Patients received medication to target episodes of breakthrough cancer pain, comprising either titrated doses of Actiq paired with placebo capsules or morphine sulfate immediate release (MSIR) capsules paired with placebo lozenges. Efficacy assessment conducted at 15, 30, 45 and 60 minutes showed mean pain intensity scores were significantly better with Actiq than MSIR at all time points and mean pain intensity difference scores also favoured Actiq at all time points. Actiq also demonstrated significantly higher pain relief scores than MSIR at all time points. Of patients opting to enrol in an open-label follow-on study, 94% chose to continue with Actiq, compared to 6% opting for MSIR. The authors concluded that Actiq was more effective than MSIR in treating breakthrough cancer pain. Again these findings were entirely consistent with the description of the pharmacodynamic properties of Actiq outlined in section 5.1 of the Actiq SPC.

ProStrakan stated that there were no head to head studies comparing the onset of action of Abstral v Actiq. As part of their initial training and induction programme the MLE team had been fully trained on the onset of action data outlined above for both Abstral and Actiq.

ProStrakan submitted that its internal records showed that no proactive contact had been made between MLEs and health professionals between February 2011 and May 2012. All contact between MLEs and health professionals that occurred since the team's inception in February 2011 had been as a response to an unsolicited request received from a health professional.

PANEL RULING

The Panel noted that the complainant was anonymous and non contactable and that, as set out in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and, like all complaints, judged on the evidence provided by the parties. The complainant had submitted no material to support his/her position. The Panel also noted the difficulty of dealing with complaints based on one party's word against the other.

The Panel considered that companies had to be extremely careful in ensuring that their medicines were not promoted for unlicensed indications. The role of MLE staff and the like needed to be very carefully controlled with detailed instructions. Guidance in this regard had recently been published in the PMCPA guidance on Clause 3 of the Code.

The Code defined a representative in Clause 1.6 as anyone calling on members of the health professions and administrative staff in relation to the promotion of medicines. This was a wide definition and could cover the activities of those employees that companies might not call representatives. Clause 1.2 defined 'promotion' as 'any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines'.

The Panel noted that the parties' accounts differed. The complainant stated that he/she had agreed to see an MLE who showed him/her data relating to studies in breakthrough cancer pain and was interested in his/her prescribing of a competitor medicine (fentanyl lozenge (Actiq) produced by Cephalon) in the specialist burns unit. The MLE compared the two medicines in relation to speed of action and related this to dressing changes and movement. The complainant alleged that the MLE had no data to support the use of Abstral in this cohort of patients. ProStrakan had submitted that its procedures only permitted MLEs to interact with burns units following an unsolicited request for information from that individual. Proactive, routine and unsolicited discussion of the off-label use of Abstral was prohibited by ProStrakan. ProStrakan had also submitted that the MLE team did not discuss both licensed and unlicensed use of Abstral in the same call. If a health professional asked an unsolicited question about the licensed use of Abstral during a discussion of off-licence use the MLE would answer that question.

The Panel further noted ProStrakan's submission that between February 2011 and May 2012 its MLE team had received 432 requests to respond to health professionals regarding the use of ProStrakan's products; three of these related to the use of Abstral in burns patients. In all cases these interactions had been prompted by requests for information by the health professional. ProStrakan had stated that it was in the process of assessing a proposal for an investigator sponsored trial submitted by a physician who worked in a burns unit and an MLE had discussed this with the physician and assisted in the preparation of the application to ProStrakan. The study proposal was initiated by the health professional concerned.

The Panel noted ProStrakan's submission that its MLE team was a field based extension of its medical information function. On reviewing the MLE job description, the Panel noted the role was split into

two, a reactive part (referred to in ProStrakan's response) and a proactive part which was made up of two functions; firstly to engage with stakeholders regarding within licence scientific data in a balanced, non-promotional way and secondly to proactively contact external stakeholders in relation to scientific publication, clinical studies, disease awareness and non promotional new data. To this extent, the Panel considered that this role went beyond that of a medical information department. The Panel further noted the informal guidance on Clause 3 of the Code issued by the Authority that stated:

> 'If the medical and scientific liaison executives and the like call upon health professionals and/or appropriate administrative staff to discuss diseases, and there is no reference either direct or indirect to specific medicines, then this activity is covered by an exemption to the definition of promotion given in Clause 1.2 of the Code. This states, *et al*, that the term promotion does not apply to statements relating to human health or disease provided there is no reference either direct or indirect to specific medicines.
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> If specific medicines are referred to either directly or indirectly, then the activity could not take the benefit of that exemption and could be likely to be seen as promotion of those medicines'.

The Panel thus considered that one aspect of the MLE role as described in the job description was likely to involve the promotion of ProStrakan medicines. In the Panel's view the job description meant that MLEs would call proactively on health professionals and this may have included the call upon the complainant. ProStrakan had not commented on the discussion regarding fentanyl lozenges.

The Panel considered that the parties' accounts differed and it was not possible to determine where the truth lay. On the very limited information provided by the complainant it was not possible for ProStrakan to identify the MLE/representative involved. It was not possible to contact the complainant for more information. The Panel considered that the complainant had not established his/her case on the balance of probabilities. No breach of Clauses 3.2, 9.1, 15.2, 15.9 and 2 was ruled.

During its consideration of this case the Panel further noted ProStrakan's submission that there were no training materials, briefing documents or any other items produced for the MLE team that discussed the use of Abstral in burns patients. However, ProStrakan had also submitted that the MLE team had, between February 2011 and May 2012, responded to three requests from health professionals for information on the use of Abstral in burns patients. The Panel was very concerned that the MLEs had responded to such requests apparently in the absence of any relevant training. The Panel considered that ProStrakan should, as a matter of some urgency, review the role and training provided to MLEs in relation to the requirements of the Code.

Complaint received **10 May 2012**

Case completed **22 June 2012**