CASE AUTH/1892/9/06

MEMBER OF THE PUBLIC v PROSTRAKAN

Rectogesic press release

A member of the public complained about the following statement in a press release issued by ProStrakan announcing the outright purchase of worldwide rights to, *inter alia*, Rectogesic (glyceryl trinitrate (GTN) rectal ointment):

> **'Rectogesic is a 0.4% topical nitroglycerin ointment indicated for the treatment of pain associated with chronic anal fissures. It is the only prescription medicine licensed specifically for the relief of this condition.**
>
> **Rectogesic works by relaxing the vascular smooth muscle around the anal canal leading to the dilation of peripheral arteries and veins, aiding the healing of the fissure. It is estimated that at any one time up to 800,000 individuals suffer from anal fissures in the EU.'**

The complainant noted that Rectogesic was not indicated for the healing of anal fissures; it was indicated for pain relief in chronic anal fissures. The statement referred to the licensed indication for Rectogesic but the second paragraph implied efficacy for the product which it did not possess and which was outside its licence. A breach of the Code was alleged.

The Panel noted that the main part of the press release stated the indication for Rectogesic ie the treatment of pain associated with chronic anal fissure. The statement at issue relating to the healing of anal fissures, was at the end of the press release in the 'Notes to Editors'.

The Panel noted that Section 5.1 of the summary of product characteristics (SPC) gave a pharmacodynamic explanation as to why GTN ointment might heal fissures, but nonetheless Rectogesic was not so licensed. The Panel considered that the statement that Rectogesic aided 'the healing of fissures' was inconsistent with the particulars listed in the SPC and thus inaccurate in that regard; high standards had not been maintained. Breaches of the Code were ruled. As the press release consisted mainly of financial information and did not promote Rectogesic *per se* and therefore did not promote an unlicensed indication the Panel ruled no breach of the Code and this was upheld on appeal by the complainant.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure. This ruling was upheld on appeal by the complainant.

A member of the public complained about a press release issued by ProStrakan Group Plc announcing the outright purchase of worldwide rights to, *inter alia*, Rectogesic (glyceryl trinitrate (GTN) rectal ointment).

COMPLAINT

The complainant noted that an earlier complaint, Case AUTH/1826/4/06, had not been upheld. He had been concerned that in a newspaper article ProStrakan was seeking to promote Rectogesic for unlicensed indications such as healing of anal fissures, or pain relief in acute fissures, whereas it was only indicated for pain relief, and then only in chronic anal fissures. A breach of Clause 3.2 had been alleged. In its ruling the Panel had noted that: 'The statement that Rectogesic was an ointment for the treatment of anal fissures was not in quotation marks in the article but was attributed to ProStrakan. The article was misleading in this regard but the Panel did not consider this was the responsibility of ProStrakan. In the absence of any detail of what ProStrakan said to the journalist no breach of the Code was ruled'. The complainant understood this ruling to mean that the Panel agreed with him that the article was misleading but that there was insufficient evidence to support the contention that ProStrakan had conveyed this false impression.

The complainant noted that a press release issued by ProStrakan on 27 September (www.ProStrakan.com/latest_351.php) which dealt with the proposed acquisition by ProStrakan of the global rights to Rectogesic from an American company called Cellegy, contained the following:

> 'Rectogesic is a 0.4% topical nitroglycerin ointment indicated for the treatment of pain associated with chronic anal fissures. It is the only prescription medicine licensed specifically for the relief of this condition.
>
> Rectogesic works by relaxing the vascular smooth muscle around the anal canal leading to the dilation of peripheral arteries and veins, aiding the healing of the fissure. It is estimated that at any one time up to 800,000 individuals suffer from anal fissures in the EU.'

The complainant alleged that the press release was in breach of Clause 3.2 because Rectogesic was not indicated for the healing of anal fissures. On this occasion the company could not deny responsibility. The statement did refer to the licensed indication for Rectogesic but the second paragraph implied efficacy for the product which it did not possess and which was outside its licence ie healing. This was confirmed by reference to the Scottish Medicines Consortium (SMC) report on its rejection of Rectogesic. According to the complainant the report stated: 'The company provided details of two unpublished dose-finding trials, the results from which were provided in confidence. The first dose-finding study was principally designed to assess healing rates, which is outside the product licence'.

The complainant also noted there was no mention anywhere in the Rectogesic summary of product characteristics (SPC) of its use as a treatment to aid the healing of anal fissures. Section 5.1 discussed the effects on relaxation of the anal sphincter and improvements in blood flow but there was no mention of healing.

In addition to Clause 3.2 cited by the complainant, the Authority also asked the company to respond in relation to the requirements of Clauses 2, 9.1 and 20.2 of the Code.

RESPONSE

ProStrakan explained that the press release had been distributed to the Stock Exchange and posted on the company website; as a publicly listed company ProStrakan was legally bound to inform its shareholders of price sensitive information. The company knew that prescription only medicines should not be advertised to the public, as could be seen from the nature, tone and content of the press release it was providing information to institutions and shareholders. ProStrakan appreciated the press release was in the public domain and as such the information contained within was balanced, factual and non-promotional, therefore, it did not seem appropriate for this to be dealt with under Clause 3.2 of the Code.

ProStrakan stated that the indications for Rectogesic were clearly stated in the second paragraph of the main text ('Rectogesic was launched in the UK in May 2005 as the only prescription only product approved for the treatment of pain associated with chronic anal fissure.') and repeated in the 'Notes to Editors' ('Rectogesic is 0.4% topical nitroglycerin ointment indicated for the treatment of pain associated with chronic anal fissures. It is the only prescription medicine licensed specifically for the relief of this condition.') as noted by the complainant.

The press release clearly identified the business importance of the information, it did not encourage members of the public to ask for a prescription and was non-promotional.

The detail of the mode of action of Rectogesic outlined within the 'Notes to Editors', explained a well-accepted principle of GTN action. Schouten *et al* (1994) was the first to demonstrate the ischaemic nature of chronic anal fissures. The publication of the landmark study by Lund *et al* (1997) demonstrated that as a nitric oxide donor GTN caused reversible relaxation of the anal sphincter improving anodermal blood flow and improving the environment for healing. ProStrakan provided a letter from Lund written to the SMC as part of a package of data and evidence for its consideration. This provided a very clear summary of the current situation with respect to Rectogesic in clinical practice, which was reinforced by a recently published treatment algorithm (Lund *et al* 2006).

ProStrakan submitted that the press release was of significant business importance and was non-promotional, with the indication for Rectogesic clearly stated twice. The mode of action of Rectogesic was simply explained in the 'Notes to Editors' as chronic anal fissures was a very uncommon problem. This information was presented in an open, balanced and fair way, with no implication of 'off licence' use as this was a non-promotional communication. ProStrakan did not consider that the press release breached Clause 3.2 of the Code or Clauses 2, 9.1 and 20.2.

PANEL RULING

The Panel noted that the press release announced the outright purchase of worldwide rights to, *inter alia*, Rectogesic. The body of the piece stated that Rectogesic was launched in the UK in May 2005 as the only prescription product approved for the treatment of pain associated with chronic anal fissures. In a section at the end of the press release, headed 'Notes to Editors', it was stated that Rectogesic was indicated for the treatment of pain associated with chronic anal fissures and that the product worked by relaxing vascular smooth muscle around the anal canal leading to the dilation of peripheral arteries and veins, aiding the healing of the fissure.

The Panel noted that the Rectogesic SPC stated that the therapeutic indication was 'relief of pain associated with chronic anal fissure'. Section 5.1 of the SPC, pharmacodynamic properties, noted that a link between internal anal sphincter hypertonicity and spasm and the presence of anal fissure had been established. In patients whose fissures healed following sphincterotomy a reduction in anal pressure and improvement in anodermal blood flow was demonstrated. Topical application of GTN relaxed the anal sphincter, resulting in a reduction in anal pressure and an improvement in anodermal blood flow. Notwithstanding this pharmacodynamic explanation as to why GTN ointment might heal fissures, Rectogesic was not so licensed; it was only licensed for the relief of pain. In that regard the Panel considered that the statement that Rectogesic aided 'the healing of fissures' was inconsistent with the particulars listed in the SPC and thus inaccurate in that regard. A breach of Clause 20.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel ruled no breach of Clause 3.2 as the press release consisted mainly of financial information and did not promote Rectogesic *per se* and therefore did not promote an unlicensed indication. This ruling was appealed.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure. This ruling was appealed.

APPEAL BY COMPLAINANT

The complainant disagreed with ProStrakan's contention, and the Panel's ruling that the press release did not constitute promotion. ProStrakan had stated that the nature, tone and content of the press release demonstrated that it had provided information to institutions and shareholders. The Panel noted in its ruling that the press release consisted mainly of financial information and did not promote Rectogesic *per se* and therefore did not promote an unlicenced indication. However, the complainant noted that on the homepage of the ProStrakan website (www.ProStrakan.com) there was a prominent box headed 'Latest Developments' (please note that it was not headed 'Latest *Financial* Developments') within which was scrolling text which advertised the company's latest press releases. Press releases of all types were posted in this box, including the one at issue. At the top of the home page was a list of sections within the website including one entitled 'Investor Relations' which contained lots of financial information about the company. It also contained a menu on the left hand side of the page which included 'press releases'. Thus, if, as ProStrakan had

stated, posting this press release in this way on its website was because it was legally bound to inform its shareholders of price sensitive information, why did it not just post it in the press release section of its 'Investor Relations' section of its website? Surely this was a much more targeted and specific means of informing investors about financial events. ProStrakan might argue that posting the press release on the front page where everyone could see it was a more certain way of drawing the attention of shareholders to this important financial information. So then why did ProStrakan not advertise all of its financial press releases on the front page of its website? For example, the press releases posted on the 'Investor Relations' section of the website included one which dealt with share options recently issued to directors and managers of the company and was presumably also released for the purpose of providing information to institutions and shareholders ('ProStrakan Group plc Share Plans', 13 October 2006). Why was one of these press releases posted prominently on the home page of the company's website and the other not. The complainant alleged that it was because the press release at issue was being used to advertise prescription products. If this was the case and if, as already agreed, the document did not accurately reflect the licensed indication, then surely this constituted a breach of Clause 3.2. Therefore the complainant appealed the Panel's ruling of no breach of Clause 3.2.

The complainant noted Clause 2 and on reading ProStrakan's response had become increasingly concerned about the company's behaviour. ProStrakan had stated that the paper 'An evidence-based treatment algorithm for anal fissure' (Lund *et al* 2006) reinforced the current situation with respect to Rectogesic. The complainant found this to be an interesting description of a document which discussed unlicensed applications of topical nitrates. For example:

Page 2, paragraph 2: 'When used in the treatment of patients with chronic anal fissure, topical nitrates lead to healing in approximately two-thirds of patients'

Page 2, paragraph 5: 'Little is reported about recurrence rates after healing with nitrates'

Page 3, paragraph 2: 'On diagnosis of anal fissure, first line treatment with topical nitrates or calcium channel blockers should begin'. Rectogesic was only indicated for the relief of pain associated with chronic anal fissures.

Page 3, paragraph 3: 'Those unhealed but asymptomatic or with notable symptomatic improvement may be offered a further 6-8 weeks of topical therapy'. Rectogesic was not indicated for patients without pain.

Page 2, paragraph 3 : 'Most studies of GTN have used 0.2% ointment. Dose finding studies have now found that a 0.4% concentration may be more effective and it is this concentration which is used in commercially available GTN ointment'. Rectogesic contained 0.4% GTN.

That ProStrakan should use this document to defend its advertising of an unlicensed use of Rectogesic was frankly astonishing. However, the astonishment was tempered somewhat by the end of the document which stated: 'Acknowledgments: Supported by an educational grant from ProStrakan'. The complainant did not know what was meant by an 'educational grant' but in light of ProStrakan's involvement in this publication and its extensive discussion of uses of topical nitrates for which Rectogesic was not licensed, the following questions needed to be asked:

In the final paragraph of the introduction Lund *et al* stated 'In December 2005, we met with the aim of developing an evidence-based treatment algorithm for anal fissure aimed to optimize the pharmacological treatment in primary care'. What involvement did ProStrakan have in arranging this meeting? For example:

Who chose the participants?, Where did the meeting take place?, Was ProStrakan involved in setting the agenda?, Did ProStrakan staff participate in the meeting? Did ProStrakan pay for this meeting?, Etc, etc, etc. What role did ProStrakan play in the writing of the manuscript?, Did it: pay for the manuscript to be written?, have any editorial input into its content?, review the manuscript prior to publication?, play any role in choosing the authors?, Etc, etc, etc.

Furthermore, the complainant noted that at a meeting of the European Society of Coloproctology in September 2006, ProStrakan sponsored a satellite symposium entitled 'European treatment algorithm for anal fissure'. The four speakers at this symposium (including the chairman) were all co-authors of Lund *et al*. The titles of the presentations at this symposium were: 'The evolution of non-surgical therapy'; 'The development of a licensed GTN'; 'The development of a European treatment algorithm'. Details of this meeting could be found at: www.escp.eu.com/includes/download.php?id=25.

Unlike ProStrakan the complainant did not consider that the Authority was the place to get into a discussion (with ProStrakan or its advisors) as to whether Rectogesic should be licensed for healing of anal fissures. The complainant stated that, for one thing, he had no expertise in this area! The right place to do that was with the regulatory authorities. If ProStrakan had sufficient data to get the indication licensed then it should do so. That it had failed to do so did not give it the right to either claim it anyway or to support publications which claimed it. Therefore, the complainant alleged that the cumulative effect of the above was to constitute a breach of Clause 2 and the appeal was on this basis.

COMMENTS FROM PROSTRAKAN

ProStrakan submitted that it had clearly outlined the rationale for the press release as non-promotional in nature and not in breach of Clauses 2 and 3.2, it therefore agreed with the Panel's ruling. The financially important nature of the material in relation to the company's expansion into the US was obviously significant. It was posted on the front page website and a link from the investors section where all other non share price sensitive information was located.

ProStrakan noted that in its response to the Clause 9.1 and 20.2 allegations, it had presented an overview of the published evidence regarding the treatment of chronic anal fissures in an editorially independent paper authored by leading European experts in the management of this condition (Lund *et al*). This paper was in line with all 'educational grants'. In addition to the other references previously provided ProStrakan submitted that it had provided a clear overview of the current data and management issues in this area in the context of its response to the original complaint.

FURTHER COMMENTS FROM THE COMPLAINANT

With regard to the alleged breach of Clause 3.2, the complainant noted that ProStrakan had added very little. With regard to Clause 2 the complainant noted that ProStrakan continued to contend that it had merely provided an overview of the current data, management issues and published evidence relating to anal fissures. Its overview was unbalanced, but the complainant did not possess the expertise to argue this point. However, the company's opinions about the role of Rectogesic in the healing of anal fissures, interesting though they might be, should not take precedence over the authorities responsible for licensing the medicine. Rectogesic did not have a licence for fissure healing. Furthermore, it appeared that the medicine (known as Cellegesic in the US) had been refused a licence by the US government for either healing or pain. Indeed, the press release at issue, stated:

> 'In July, the Food and Drug Administration (FDA) granted Cellegesic approvable status in the US, conditional upon a further clinical trial being successfully conducted. ProStrakan will initiate this trial as soon as practicable following closure of the acquisition. Upon successful completion of the trial, the results would be submitted to the FDA with a view to pursuing full US approval.'

The complainant referred to the FDA websites, in particular to section 1 of a 2004 FDA report on Cellegesic and the minutes of an FDA meeting to discuss the Cellegesic application which took place on 25 April 2006. Dr Lund spoke to the FDA on behalf of Cellegy at this meeting. At the conclusion of the meeting the FDA decided that Cellegesic could only be approved for the treatment of fissure pain 'pending another study of effectiveness'.

The complainant alleged that importantly, both these documents stated clearly that a company sponsored clinical study conducted specifically to determine whether this medicine had any effect on the healing of anal fissures showed clearly that it did not. Thus, these documents indicated strongly why Rectogesic did not have a licence for the healing of anal fissures and why it should not be promoted as such by ProStrakan, either overtly or indirectly.

The complainant noted the specific questions about the algorithm publication; questions which were set out in the appeal and which were not addressed by ProStrakan. The complainant hoped that these questions would be raised at the appeal.

APPEAL BOARD RULING

The Appeal Board noted that ProStrakan had accepted the Panel's rulings of breaches of Clauses 9.1 and 20.2.

The Appeal Board upheld the Panel's ruling of no breach of Clause 3.2 as the press release was not a promotional item; it consisted mainly of financial information and thus did not promote Rectogesic *per se* for an unlicensed indication. The appeal on this point was unsuccessful.

The Appeal Board did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure. The Appeal Board thus upheld the Panel's ruling of no breach of Clause 2. The appeal on this point was also unsuccessful.

Complaint received	**29 September 2006**
Case completed	**7 December 2006**