CASE AUTH/2417/6/11

PRIMARY CARE TRUST HEAD OF MEDICINES MANAGEMENT v SERVIER

Promotion of Procoralan

A primary care trust (PCT) head of medicines management alleged that Servier had promoted Procoralan (ivabradine) for the unlicensed indication of heart failure. Procoralan was indicated for the symptomatic treatment of chronic stable angina.

Emails about the use of ivabradine in heart failure which had passed between the PCT and a medical liaison specialist (MLS) with Servier were provided. In one of the emails the MLS explained that he was not part of the sales force team and that his role was to deal with the non licensed indications for Procoralan. Details of the licensed indication for Procoralan were given as well as information about Servier's application for an extension for heart failure. The MLS stated in his email that he had seen many local consultant cardiologists and the responses had been very positive. 'In some areas clinicians are already using the product (off licence) in heart failure. As a consequence I felt it appropriate to make contact, to ensure that ... you would have an opportunity to be brought up to date with the most recent data ...'. This email ended with an invitation to meet to discuss heart failure, ivabradine and the patient pathway. The recipient replied by copying in the medicines management lead pharmacist. The MLS replied and suggested a joint meeting to which he would 'bring some data and modelling tools'. The medicines management lead noted that Procoralan had to be licensed for heart failure before it could be funded and that the contraindications and cautions in the summary of product characteristics (SPC) referred to heart failure and that GPs could not be expected to prescribe a contraindicated therapy. A number of steps were set out that needed to be taken before the matter could be discussed. In the final email the MLS referred to the licensed status of Procoralan and noted there was a lot of published data in respect of heart failure but he had never suggested it be prescribed for heart failure at the moment. He wanted to bring everyone up to speed, to look at existing pathways and to report on the thinking of consultants in cardiology/care of the elderly.

The detailed response from Servier is given below.

The Panel noted the licensed indications for Procoralan. It also noted that the special warnings and precautions for use section of the SPC stated, under headings of 'Special warnings' and 'Chronic heart failure' that heart failure must be appropriately controlled before ivabradine treatment was considered. Ivabradine was contraindicated in moderate to severe heart failure and should be used with caution in patients with mild heart failure.

The Panel noted that Servier expected to gain a chronic heart failure indication for Procoralan towards the end of 2011.

The Panel noted that 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'. This was followed by a list of activities within that definition and a number that were not. There was an exemption to the definition of promotion for 'replies made in response to individual enquiries from members of the health professions or appropriate administrative staff'. This exemption related to unsolicited enquiries only and allowed pharmaceutical companies to answer specific questions from health professionals and appropriate administrative staff. Questions about unauthorized medicines or unauthorized indications frequently came up in this context. To ensure that the exemption was only used in relation to genuine enquiries the word 'unsolicited' was used. This was to clearly separate the promotion of medicines from the role of medical information departments.

The Code defined a representative as a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines.

The supplementary information to the Code stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion. In this regard the context in which the exchange took place and the audience would be important factors in determining whether the activity was acceptable under the Code. The proactive provision of information about the unauthorized use of a medicine was very likely to be seen as promotion.

The supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes, referred to various NHS organisations

and their need to establish their likely budgets two to three years in advance in order to meet Treasury requirements and for them thus to receive advance information about the introduction of new medicines, or changes to existing medicines, which might significantly affect their future level of expenditure. It was noted that when this information was required, the medicines concerned would not be the subject of marketing authorizations (though applications would often have been made) and it would thus be contrary to the Code for them to be promoted. The supplementary information included the requirement that advance notification must include the likely cost and budgetary implications which must make significant differences to the likely expenditure of health authorities etc.

The Panel noted that there were two issues to be considered, firstly whether the MLS who had written the emails had acted in accordance with the Code and secondly whether the company's materials and instructions were in accordance with the Code.

Servier provided a copy of what it described as an access letter for the MLS team to use to contact budget holders in the NHS about Procoralan which stated that Servier would shortly apply to extend the current licensed indication and if successful a new indication for chronic heart failure would be expected towards the end of 2011. The letter detailed the current indication and referred to the recipient as someone who had a role in policy making or deciding budgets for cardiovascular disease within the NHS. The letter also stated that the Code advised that advance budgetary information might be provided to policy influencers and those responsible for budgetary decisions to aid in future planning. The company wished to provide the relevant clinical and budgetary data relating to the product to assist the planning process and that the recipient would be contacted by the MLS to arrange a meeting. The date of preparation of the access letter was August 2010. The approval form for the letter described it as a 'budget impact letter'.

The Panel noted that advanced information could only be supplied if the product had a significant budgetary implication. The Panel queried whether the introduction of Procoralan for chronic heart failure would have a significant budgetary implication. The access letter did not refer to the budgetary implication. In the Panel's view if this condition was not met then advanced notification was not permitted under the Code.

It appeared to the Panel that Servier might have carried out an advance notification process for the unlicensed indication since at least August/September 2010. However if the licence was expected by the end of 2011 the timeframe appeared to be inconsistent with that stated in the relevant supplementary information as being 2 – 3 years before launch. The Panel queried whether the information had been supplied early enough such that budget holders etc could be reasonably expected to act upon it.

The MLS job description set out the main purpose of the job which was to: provide field-based medical information services; respond to medical enquiries; manage non interventional studies and deliver medical and educational goods and services and support the cardiovascular key account managers including provision of relevant clinical and scientific training. The principal responsibilities in the job description included the above and in addition the non-promotional exchange of medical and scientific information. This was described as supporting the legitimate exchange of scientific and medical information with cardiovascular health professionals through advisory boards and 1:1 visits. This would include advance notification of new products or product changes as set out in the Code.

The Panel noted that the MLS job description had amalgamated a number of key activities each of which was subject to different requirements in the Code. This was not helpful and in the Panel's view could lead to confusion as to the precise nature of any activities undertaken. The Panel noted that it had previously been decided that it was not necessarily unacceptable to have employees focussing on the provision of information prior to the grant of the marketing authorization or prior to the licensing of an indication. The arrangements and activities of such employees had to comply with the Code and they should be comprehensively briefed about the Code. Companies needed to ensure that in this difficult area the arrangements and activities were very carefully controlled and managed. The importance of documentation and instruction could not be overestimated.

The Panel noted that the MLS team was provided with three presentations, for use 'on request of medical enquiries': 'Ivabradine in Heart Failure', 'Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial' and 'SHIFT-PRO: Patient Reported Outcomes Quality of Life SubStudy'. The second slide of each presentation detailed the licensed indication for Procoralan. This was followed by the statement that the use of ivabradine outside this indication was unlicensed and could not be recommended. A statement that heart failure must be appropriately controlled before considering ivabradine treatment was followed by details of the contraindication and caution in the Procoralan SPC. The second presentation stated that the contraindication in moderate to severe heart failure was due to lack of data. This reason was not included in the SPC. The

presentations had been certified, the first presentation as promotional material and the other two as non-promotional material.

The MLS team was also given advanced budgetary notification material and training on the calls. Two consecutive slides detailed the supplementary information to the Code which provided the basis on which advanced notification could be given. Some of these were highlighted in bold underlined type but not the need for the likely cost and budgetary implications to be indicated and to be significant. The MLS team was also provided with a cost effectiveness analysis presentation for use of ivabradine in heart failure in the UK based on the SHIFT trial results. Although the contraindication for moderate to severe heart failure was included in slide 2, the caution in the SPC regarding mild heart failure was not. The presentation gave information about the cost per QALY (quality adjusted life year). According to the certificate the presentation had been approved for use following an unsolicited request from a health professional about the cost effectiveness of Procoralan in heart failure. The MLS team was also provided with a budget impact model for ivabradine in heart failure based on the SHIFT trial which had been approved for use in response to an unsolicited request for information on the cost effectiveness of Procoralan in heart failure. The Panel queried whether these materials constituted the 'data and modelling tools' which the MLS in question had proactively offered.

General guidance on responding to enquiries about heart failure was provided to key account managers and MLS staff. In responding to questions about the SHIFT study key account managers were instructed to generally include mention of the ivabradine licensed indication and that following the results the company planned to apply for a heart failure licence. Key account managers were then instructed to say that they could not discuss this further but should further information be required the preferred option for follow up was for a cardiovascular MLS to arrange a meeting.

In relation to the company's materials and instructions the Panel was extremely concerned about the activities with regard to the advanced notification of the use of Procoralan in heart failure. The Panel considered that on the evidence before it the MLS activity in this regard did not meet the conditions set out in the Code in relation to the need to demonstrate a significant budgetary implication and supply information about it. Servier's response did not show that the use of Procoralan in heart failure had a significant budgetary impact and no details had been provided in the access letter about the likely cost and budgetary implication as required in the relevant supplementary information.

The Panel did not consider that the MLS's role was non-promotional. Servier had not limited the activities to responding to unsolicited requests. The company had arranged for its staff to proactively call upon health professionals and others to raise awareness of the use of Procoralan for an unlicensed indication. In that regard the Panel noted that in the last 6 months, the MLS in question had contacted 57 health professionals/budget holders about the use of ivabradine in heart failure. The company's activity amounted to the promotion of Procoralan for an unlicensed indication, heart failure, which was the subject of a contraindication or caution in the SPC. A breach of the Code was ruled. The Panel considered that high standards had not been maintained. A breach of the Code was ruled. Given its ruling that the MLS role was promotional, the failure to comply with the relevant requirements of the Code was ruled in breach of the Code.

The Panel noted that Clause 2 of the Code was a sign of particular censure and reserved for such. The Panel considered that the activity at issue amounted to a softening of the market for using Procoralan in heart failure, a condition which was the subject of a contraindication or caution in the SPC. This brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

In relation to the emails provided by the complainant the Panel considered that the MLS in question had promoted Procoralan for an unlicensed indication. In this regard it noted that the MLS had seen many consultant cardiologists whose responses had been positive and that some were already using the product off licence in heart failure. A breach of the Code was ruled. The emails did not mention that the product was contraindicated or the subject of an SPC caution in certain types of heart failure. This potentially had a negative impact on patient safety. High standards had not been maintained and a breach of the Code was ruled. [This was the only breach ruling accepted by Servier – all of the others were appealed]. The Panel noted its ruling of a breach of Clause 2 in relation to the company's activities and decided in the circumstances that the conduct of the MLS in question did not warrant a separate ruling in relation to Clause 2.

The Panel considered that overall Servier's actions were unacceptable; given that no budgetary impact for ivabradine in heart failure was stated, the MLS's activities did not constitute advance notification of a new indication. Overall the Panel considered that Servier's activity amounted to the promotion of ivabradine for an unlicensed indication. The Panel decided to report the company to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

Upon appeal by Servier the Appeal Board noted

that the promotion of a medicine prior to the grant of its marketing authorization was prohibited and that promotion of a medicine must be in accordance with the terms of its marketing authorization and not inconsistent with its SPC. The supplementary information to the Code set out guidance in relation to certain situations including the provision of advanced notification of new products or product changes. This supplementary information included a requirement that such information must include the likely cost and budgetary implications and this must be such as to make a significant difference to the likely expenditure of health authorities, trusts and the like.

The Appeal Board noted that the emails at issue sent by the MLS did not discuss the anticipated cost or the budgetary implications of using Procoralan for heart failure. The Appeal Board noted that one of the MLS's emails stated that 'I have seen many consultant cardiologists in the [local] region and the responses have been very positive. In some areas clinicians are already using the product (off licence) in heart failure. As a consequence I felt it appropriate to make contact, to ensure that ... you would have an opportunity to be brought up to date with the most recent data that we have.' The Appeal Board considered that the very positive description of the heart failure indication in the absence of any discussion either of the budgetary implications or the significance of the difference in expenditure meant that the MLS had promoted Procoralan for an unlicensed indication. The email in question could not take the benefit of the exemption for advance notification set out in the supplementary information to the Code. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted that 'representative' was defined in the Code as 'a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines.' It considered that its ruling that the product had been promoted for an unlicensed indication did not mean that it considered that the MLS job description described a representative's role as defined in the Code. The Appeal Board thus ruled no breach of the Code as the clause at issue applied to the conduct of representatives. The appeal on this point was successful.

The Appeal Board noted that advanced information about an unlicensed indication could only be supplied if such use of the product had a significant budgetary implication and the information included details of the likely cost and budgetary implication. The relevant supplementary information to the Code set out detailed conditions. The Appeal Board noted Servier's submission for the appeal that its Budget Impact Model, based on the results of the SHIFT study (Swedburg *et al*), showed a typical net annual cost of treating heart failure with Procoralan of £3,000-£9,000 per 100,000 head of population. The Appeal Board noted in the email correspondence the head of prescribing and medicines management stated that the estimated cost to the PCT of using Procoralan in a suitable population was around £75,000/year but there would be 'therapeutic creep' and so the cost would be considerably more. The head of prescribing and medicines management also stated that the patients in the study were not on optimum doses of beta-blocker. The Appeal Board considered that NHS managers were likely to regard such potential increases in budgetary requirements as significant particularly given the current economic environment. The Appeal Board considered that the licence extension application for Procoralan for heart failure satisfied the condition in the supplementary information to the Code that advanced notification information might be provided for '... a product which is to have a significant addition to the existing range of authorized indications ...'.

The Appeal Board did not consider that starting the advanced notification in August/September 2010 for changes to the licence expected by the end of 2011 was unacceptable. The Appeal Board noted Servier's submission for the appeal that the licence was now expected in April/June 2012. The Appeal Board noted the access letter discussed the ivabradine licence application to add an indication for chronic heart failure. The letter detailed the current licensed indication and stated that the Code advised that advanced budgetary information might be provided to policy influencers and those responsible for budgetary decisions to aid future planning. The Appeal Board considered that the purpose of the letter was to determine if recipients were responsible for budgetary decisions and if so to provide '... the relevant clinical and budgetary data relating to this product to assist your planning process'. The letter also stated that the author intended to contact the recipient to organise a meeting.

The Appeal Board considered that advanced notification was a difficult area and care was needed to satisfy the relevant requirements of the supplementary information to the Code. The Appeal Board was concerned about some of the claims made in material used by the MLSs and also about their proactive contact of key opinion leaders. Nonetheless the Appeal Board did not consider that the company's activity amounted to the promotion of Procoralan for an unlicensed indication. The Appeal Board also noted that the complainant had emphasised the role of the individual MLS as evidenced by the email trail rather than activities undertaken by the company. The Appeal Board ruled no breach of the Code. The appeal on this point was successful.

The Appeal Board noted the rulings of a breach of the Code in relation to the MLS in question. The Appeal Board considered that Servier should have more closely controlled its MLS team. High standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

During its consideration of this point the Appeal Board noted Servier's recent decision that emails sent by the MLS team be copied to their manager but queried whether this on its own introduced sufficient control.

The Appeal Board noted its rulings above and considered that a ruling of a breach of Clause 2 was not warranted and so no breach of that clause was ruled. The appeal on this point was successful.

Given its rulings the Appeal Board decided to take no further action in relation to the report from the Panel.

A primary care trust (PCT) head of medicines management alleged that Servier had promoted Procoralan (ivabradine) for the unlicensed indication of heart failure. Procoralan was otherwise indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm, in adults unable to tolerate or with a contraindication to the use of beta-blockers or in combination with beta-blockers in patients inadequately controlled with an optimal beta blocker dose and whose heart rate was greater than 60 beats per minute.

COMPLAINT

The complaint was prompted by emails about the use of ivabradine in heart failure which had passed between the PCT and a medical liaison specialist (MLS), cardiovascular. Copies were provided.

The email trail started with emails from the MLS to the chief executive at a community interest company (CIC) in relation to a presentation by the chief executive at a meeting organised by the MLS. The second email asked for contact details so that the MLS could contact someone in CIC to discuss heart failure pathways and possible heart failure audits. The chief executive suggested the director of clinical transformation who was in the process of being appointed. The MLS contacted the director of clinical transformation in June explaining that he was not part of the sales force team and that his role was to deal with the non licensed indications for Procoralan. He referred to his previous role in the NHS. Details of the licensed indication were given as well as information about Servier's application for an extension for heart failure which was expected by the end of 2011 or early 2012. The MLS stated in his email that he had seen many consultant cardiologists in the region and the responses had been very positive. 'In some areas clinicians are already using the product (off licence) in heart failure. As a consequence I felt it appropriate to make contact, to ensure that as the director of clinical transformation, you would have an opportunity to be brought up to date with the most recent data …'. This email ended with an invitation to meet to discuss heart failure, ivabradine and the patient pathway. The recipient replied by copying in the medicines management lead pharmacist. The MLS replied and suggested a joint meeting to which he would 'bring some data and modelling tools'. The medicines management lead noted that in order to assure funding for ivabradine in heart failure the product needed to be licensed for the indication and that the promotion of an unlicensed indication was prohibited. The contraindications and cautions in the Procoralan summary of product characteristics (SPC) in relation to use in heart failure were mentioned and that GPs could not be expected to prescribe a contraindicated therapy. A number of steps were set out that needed to be taken before the matter could be discussed. These included a review of evidence and cost effectiveness, whether the PCT would fund it, the estimated cost was £75,000 per year and there would be additional 'therapeutic creep' costs. Finally a recent study had noted that patients were not on the optimum doses of beta blocker which was current practice. In the final email the MLS referred to the licensed status of Procoralan and noted there was a lot of published data in respect of heart failure but he had never suggested it be prescribed for heart failure at the moment. His intention was to bring everyone up to speed, to look at existing pathways and to report on the thinking of consultants in cardiology/care of the elderly. The plan was to look at economic models and quality of life issues and how these impacted on present management pathways.

When writing to Servier, the Authority asked it to respond in relation to Clauses 2, 3.2, 9.1 and 15.2 of the Code.

RESPONSE

Servier regretted that this complaint had arisen. It was nonetheless grateful to both the complainant and the PMCPA for bringing the email thread to its attention. This communication was unclear and ambiguous, and hence did not meet Servier or industry standards. However, following investigation, Servier believed that the specific allegation was unfounded. Servier sought to reassure the PMCPA in this regard.

Servier attached great importance to meeting its obligations with regard to the Code and relevant regulations. It invested significantly in appropriate staff, procedures and training to ensure that this occurred. These approaches were reflected in the company organogram, standard operating procedures (SOPs), job descriptions and other documentation supplied as requested for the scrutiny and reassurance of the PMCPA.

Pre-licence communication

Pre-licence communication was allowed by Servier's procedures only in tightly-limited circumstances. These activities were always carried out by appropriately-trained, non-promotional staff within the medical affairs team. Where these staff were field-based Servier referred to them as MLS. Servier noted that this was not a 'representative' role as defined in Clause 1.6. Servier allowed pre-licence communication when it was:

– in response to unsolicited medical enquiries
– advanced budgetary notification to policy makers/budget holders, and
– the legitimate exchange of medical and scientific information (for example briefing an opinion leader for a presentation to an advisory board).

MLS responsibilities also extended to liaison related to research – both investigator-led and non-interventional studies.

The MLS at issue was a senior and respected member of the Servier MLS team and had never worked in a promotional role. His previous NHS background, together with his training records, demonstrated his suitability and preparedness for the MLS role. The MLS's immediate manager carried out field visits with him on a regular two-monthly basis. In his role as an MLS, and indeed in his career to date, his ethics and integrity had never been questioned.

The MLS covered a large area. In the last six months he had made 132 contacts (all types, including research liaison as described above) of which 69 were specifically related to ivabradine and heart failure. The heart failure-related contacts were spread across 100 organisations, covering 57 individual health professionals/budget holders.

The email thread

Clause 9.1

Servier submitted that its investigation had shown that, as might be predicted from his role and the setting, the intent of the MLS in question was to identify the relevant policy and budget holders in the new consortium structure and to engage with them regarding future planning under the advanced notification provision. Indeed the first contact was a follow-up email to a speaker from an advisory board who was chief executive of an emerging primary care consortium. Subsequent mails were the result of onward referral to a policy maker for heart failure within the new consortium and by him to the appropriate budget holder. Servier accepted this explanation as evidence that the intent of the communication was advanced notification.

However, Servier also noted that the single email thread was unclear, ambiguous and included extraneous references. In advising Servier of the complaint, the Authority had noted the use of the phrases 'bringing everyone up to speed … and report on what consultants in cardiologists/care of the elderly were thinking' and 'heart failure audits'. Servier additionally noted 'I have seen many consultant cardiologists in the [local] region and the responses have been very positive. In some areas clinicians are already using the product (off licence) in heart failure' as meriting investigation/clarification. As stated above Servier was now satisfied as to the true intent of the contacts. Servier also noted that when specifically questioned, the MLS stated that the references to clinician feedback/existing prescribing were important context for this discussion (being predictive of likely local uptake post-licence). Nevertheless both the MLS and his immediate manager accepted and understood that communication should have been clearer and more explicit in its intention. It hence fell below the standard of communication expected by Servier. In relation to Clause 9.1, Servier acknowledged that the ambiguity appeared to have resulted in misperception of the MLS's intent (as promotional) by at least one recipient. Servier hence accepted that high standards had not been maintained at all times.

Clause 3.2

Servier took this complaint extremely seriously and did not seek to minimise its importance. It highlighted that even with robust procedures, isolated anomalies might sometimes occur. However for a complaint of pre-licence promotion to be upheld Servier believed that it would be necessary to demonstrate, on the balance of probabilities, that promotion (defined in the Code as promotion of prescription, supply, sale or administration of ivabradine for heart failure) had occurred. In this regard Servier noted that the pre-licence context, the non-promotional role of the MLS in question and a sense of future planning were consistent in the communication in the thread. It was equally clear in Servier's view that engagement with these health professionals was in their roles as policy maker and budget holder at CIC respectively, and not in relation to any potential role in the prescribing or dispensing of ivabradine. Indeed the MLS in question was referred on to each contact by the precedent, commencing with the chief executive. Equally from the recipient's perspective it should be readily understood that the MLS in question was not a sales representative; this point was explicitly made in the first contact and forwarded with all subsequent communication. Lastly Servier noted that the email title 'Re: Ivabradine in heart failure' was added by one of the recipients during the correspondence, it was not written by the MLS.

Overall, Servier believed that neither the nature, purpose, nor consequence of these contacts was promotional. As a result Servier did not believe that Clause 3.2 had been breached.

Clauses 15.2 and 2

In relation to Clause 15.2 Servier observed that whilst the issue concerned communication by a Servier employee, this employee was not a 'representative' as defined by the Code. Further, following investigation Servier believed the complainant's allegation of pre-licence promotion was unfounded. Servier standards and therefore Clause 9.1 were breached in an isolated circumstance and this was regrettable. Servier did not believe however that this risked the reputation of the industry.

Actions taken by Servier

Notwithstanding his integrity and professional record the MLS in question was suspended for seven working days during the investigation of this complaint. Following the investigation, which satisfied Servier as to his intent, he had been deployed on a head office project at least until such time as Servier had completed implementation of new processes outlined below, team re-training on these, and team retraining on advanced notification and the Code.

Acknowledging a breach of Clause 9.1, Servier was acting to prevent a recurrence through new processes. These required that all emails from an MLS to a health professional (including those in commissioning groups) were copied to the national MLS manager in order to support standardised communication and compliance. The company would also require that once an appropriate policy maker or budget holder was identified, the certified advanced notification letter be used.

Additionally, the PMCPA's conclusions would be reflected in a presentation to all MLS staff regarding the context and outcomes of this complaint together with a reminder of updated Servier policy regarding pre-licence communication. A summary of the content and outcome of this complaint would also be communicated to all commercial Servier staff.

PANEL RULING

The Panel noted the licensed indications for Procoralan. It also noted that the special warnings and precautions for use section of the SPC stated, under headings of 'Special warnings' and 'Chronic heart failure' that heart failure must be appropriately controlled before ivabradine treatment was considered. Ivabradine was contraindicated in heart failure patients with NYHA functional classification III-IV and should be used with caution in heart failure patients with NYHA functional classification I-II.

The Panel noted that Servier expected to gain a chronic heart failure indication for Procoralan towards the end of 2011.

The Panel noted that Clause 1.2 of 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'. This was followed by a list of activities within that definition and a number that were not. There was an exemption to the definition of promotion for 'replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them whether of enquiry or comment, including letters published in professional journals, but only if they relate solely to the subject matter of the letter or enquiry, are accurate and do not mislead and are not promotional in nature'. Further guidance was given in the supplementary information to Clause 1.2, Replies Intended for Use in Response to Individual Enquiries, which stated:

'The exemption for replies made in response to individual enquiries from members of the health professions or appropriate administrative staff relates to unsolicited enquiries only. An unsolicited enquiry is one without any prompting from the company. In answering an unsolicited enquiry a company can offer to provide further information. If the enquirer subsequently requests additional information this can be provided and would be exempt from the Code provided the additional information met the requirements of the exemption. A solicited enquiry would be one where a company invites a person to make a request. For example, material offering further information to readers would be soliciting a request for that information. Placing documents on exhibition stands amounts to an invitation to take them. Neither can take the benefit of this exemption.'

The reason for the exemption was to allow pharmaceutical companies to answer specific questions from health professionals and appropriate administrative staff. Questions about unauthorized medicines or unauthorized indications frequently came up in this context. To ensure that the exemption was only used in relation to genuine enquiries the word 'unsolicited' was used. This was to clearly separate the promotion of medicines from the role of medical information departments.

Clause 1.6 of the Code defined a representative as a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines.

The supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under that or any other clause. In this regard the context in which the exchange took place and the audience would be important factors in determining whether the activity was acceptable under the Code. The proactive provision of information by a pharmaceutical company about the unauthorized

use of a medicine was very likely to be seen as promotion.

The supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes, stated that health authorities and health boards and their equivalents, trust hospitals and primary care trusts and groups needed to establish their likely budgets two to three years in advance in order to meet Treasury requirements and there was a need for them to receive advance information about the introduction of new medicines, or changes to existing medicines, which might significantly affect their level of expenditure during future years. It was noted that when this information was required, the medicines concerned would not be the subject of marketing authorizations (though applications would often have been made) and it would thus be contrary to the Code for them to be promoted. The supplementary information gave guidance on the basis on which such advance information could be provided including the requirement to include the likely cost and budgetary implications which must make significant differences to the likely expenditure of health authorities etc.

The Panel noted that there were two issues to be considered, firstly whether the MLS who had written the emails had acted in accordance with the Code and secondly whether the company's materials and instructions were in accordance with the Code.

Servier provided a copy of what it described as an access letter for the MLS team to use to contact budget holders in the NHS. This was headed 'Advance Budget Notification of an Application to Extend the Licensed Indication of Ivabradine' and stated that Servier would shortly apply to extend the current licensed indication for ivabradine and if successful a new indication for chronic heart failure would be expected towards the end of 2011. The letter detailed the current indication and referred to the recipient as someone who had a role in policy making or deciding budgets for cardiovascular disease within the NHS. The letter also stated that the ABPI Code advised that advance budgetary information might be provided to policy influencers and those responsible for budgetary decisions to aid in future planning. The company wished to provide the relevant clinical and budgetary data relating to the product to assist the planning process and the recipient would be contacted by the MLS to arrange a meeting. The date of preparation of the access letter was August 2010. The approval form for the letter described it as a 'budget impact letter'.

The Panel noted that advanced information could only be supplied if the product had a significant budgetary implication. The Panel queried whether the introduction of Procoralan for chronic heart failure would have a significant budgetary implication. There was no mention in the access letter of whether or not there was a significant budgetary implication. In the Panel's view if this condition was not met then advanced notification was not permitted under the Code.

It appeared to the Panel that Servier might have carried out an advance notification process for the unlicensed indication since at least August/September 2010. However if the licence was expected by the end of 2011 the timeframe appeared to be inconsistent with that stated in the relevant supplementary information as being 2 – 3 years before launch. In that regard, the Panel queried whether the information had been supplied early enough such that budget holders etc could be reasonably expected to act upon it.

The MLS (cardiovascular) job description set out the main purpose of the job which was to:

- provide field-based medical information services
- respond to medical enquiries
- manage non interventional studies and deliver medical and educational goods and services
- support the cardiovascular key account managers including provision of relevant clinical and scientific training.

The principal responsibilities in the job description included the above and in addition the non-promotional exchange of medical and scientific information. This was described as supporting the legitimate exchange of scientific and medical information with health professionals in the field of cardiovascular medicine through the organisation of advisory boards as well as 1:1 visits. This would include advance notification of new products or product changes as set out in Clause 3 of the Code.

The Panel noted that the MLS job description had amalgamated a number of key activities each of which was subject to different requirements in the Code. This was not helpful and in the Panel's view could lead to confusion as to the precise nature of any activities undertaken. The Panel noted that it had previously been decided that it was not necessarily unacceptable for companies to have employees focussing on the provision of information prior to the grant of the marketing authorization or prior to the licensing of an indication. The arrangements and activities of such employees had to comply with the Code. Such employees should be comprehensively briefed about the Code. The area was difficult and companies needed to ensure that the arrangements and activities were very carefully controlled and managed. The importance of documentation and instruction could not be overestimated.

The Panel noted that the MLS team was provided with three presentations, for use 'on request of medical enquiries': 'Ivabradine in Heart Failure', 'Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial' and 'SHIFT-PRO: Patient Reported Outcomes Quality of Life SubStudy'. The second slide of each

presentation detailed the licensed indication for Procoralan. This was followed by the statement that the use of ivabradine outside this indication was unlicensed and could not be recommended. A statement that heart failure must be appropriately controlled before considering ivabradine treatment was followed by details of the contraindication and caution in the Procoralan SPC. The second presentation stated that the contraindication in NYHA functional classification III-IV was due to lack of data. This reason was not included in the SPC. The presentations had been certified, the first presentation as promotional material and the other two as non-promotional material.

The MLS team was also provided with advanced budgetary notification material including training on the calls. Two consecutive slides detailed the supplementary information to Clause 3.1 which provided the basis on which advanced notification of new products or product changes could be given. Some of these were highlighted by the use of bold underlined type. The need for the likely cost and budgetary implications to be indicated and to be significant was not highlighted in this way. The MLS team was also provided with a cost effectiveness analysis presentation for use of ivabradine in heart failure in the UK based on the SHIFT trial results. Although the contraindication for NYHA III-IV was included in slide 2, the caution in the SPC regarding NYHA I-II was not. The presentation gave information about the cost per QALY (quality adjusted life year). According to the certificate the presentation had been approved for use following an unsolicited request from a health professional regarding the cost effectiveness of Procoralan in heart failure. The MLS team was also provided with a budget impact model for ivabradine in heart failure based on the SHIFT trial. Again this had been approved for use in response to an unsolicited request for information on the cost effectiveness of Procoralan in heart failure. The Panel queried whether these materials constituted the 'data and modelling tools' which the MLS in question had proactively offered.

General guidance on responding to enquiries about heart failure were provided to key account managers and MLS staff. In responding to questions about the SHIFT study key account managers were instructed to generally include mention of the ivabradine licensed indication and that following the results the company planned to submit to the European Medicines Agency (EMA) for a licence in heart failure. Key account managers were then instructed to say that they could not discuss this further but should further information be required the preferred option for follow up was for a cardiovascular MLS to arrange a meeting.

In relation to the company's materials and instructions the Panel was extremely concerned about the activities with regard to the advanced notification of the use of Procoralan in heart failure. The Panel considered that on the evidence before it the MLS activity in relation to advanced notification did not meet the conditions set out in the supplementary information in relation to the need to demonstrate a significant budgetary implication and supply information about it. The response from Servier did not show that the use of Procoralan in heart failure had a significant budgetary impact and no details had been provided in the access letter about the likely cost and budgetary implication as required by point iv of the relevant supplementary information.

The Panel did not consider that the MLS's role was non-promotional. Servier had not limited the activities to responding to unsolicited requests. The company had arranged for its staff to proactively call upon health professionals and others to raise awareness of the use of Procoralan for an unlicensed indication. In that regard the Panel noted that in the last 6 months, the MLS in question had contacted 57 health professionals/budget holders about the use of ivabradine in heart failure. The company's activity amounted to the promotion of Procoralan for an unlicensed indication, heart failure, which was the subject of a contraindication or caution in the SPC. A breach of Clause 3.2 was ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. Given its ruling that the MLS role was promotional, the failure to comply with the relevant requirements of the Code was ruled in breach of Clause 15.2.

The Panel noted that Clause 2 of the Code was a sign of particular censure and reserved for such circumstances. The supplementary information to that clause listed examples of activities likely to be in breach of Clause 2 including promotion prior to the grant of a marketing authorization and activities likely to prejudice patient safety. The Panel considered that the activity amounted to a softening of the market for using Procoralan in heart failure, a condition which was the subject of a contraindication or caution in the SPC. This brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

In relation to the emails provided by the complainant the Panel considered that the MLS in question had promoted Procoralan for an unlicensed indication. In this regard it noted phrases that the MLS had seen many consultant cardiologists whose responses had been positive and that some were already using the product off licence in heart failure. A breach of Clause 3.2 was ruled. The emails did not mention that the product was contraindicated or the subject of an SPC caution in certain types of heart failure. This potentially had a negative impact on patient safety. High standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel noted its ruling of a breach of Clause 2 in relation to the company's activities and decided in the circumstances that the conduct of the MLS did not warrant a separate ruling in relation to Clause 2.

The Panel considered that overall Servier's actions were unacceptable; given that no budgetary impact for ivabradine in heart failure was stated, the MLS's activities did not constitute advance notification of a new indication. Overall the Panel considered that Servier's activity amounted to the promotion of ivabradine for an unlicensed indication. The Panel decided to report the company to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY SERVIER

Servier appealed the Panel's rulings of breaches of Clauses 2, 3.2, 9.1 and 15.2 in relation to the activities of the company and Clause 3.2 in relation to the activities of the MLS in question.

Servier acknowledged that, regrettably, its usual high standards were not maintained by the MLS concerned and so it had accepted the Panel's ruling of breach of Clause 9.1 in relation to his conduct. However, Servier denied that the email correspondence at issue amounted to unlicensed promotion and therefore appealed the ruling of a breach of Clause 3.2 in relation to the individual MLS. Servier was confident of its policies, procedures and MLS team to know that this was not the purpose of the communication, and should not have been interpreted as such. Servier fully stood by the important role played by its MLSs as testified by its commitment to further strengthen its policies and procedures relating to the team. However, the Panel had apparently assumed that this single, unfortunate incident reflected serious flaws in Servier's policies and company organisation. This called into question the proportionality and the evidence basis for the ruling. Servier therefore found itself having to defend fundamental aspects of its policies and company structure with regard to its MLS team, notwithstanding that this case concerned an isolated (albeit regrettable) incident.

Servier submitted that insufficient information was provided to enable it to understand how the Panel reached its conclusions. Indeed, the Panel summarised certain aspects of Servier's material and instructions and raised certain queries, before making the extremely serious allegation that 'The company's activity amounted to the promotion of Procoralan for an unlicensed indication …'. Servier did not accept this conclusion, and did not agree that it was justified on the basis of the evidence before the Panel, or at all. It was essential for Servier to obtain clarification on what exactly the Panel had criticised and why; the uncertainty affected the everyday operations of the MLS team and reduced morale.

Servier did not have a policy or practice of promoting Procoralan (or any other product) for an unlicensed indication. Pharmaceutical companies commonly maintained a field-based medical and scientific liaison team (ie the MLS role within Servier). In Servier's experience, such a team brought significant benefit to NHS health professionals and thus to public health. There was real value in having a field-based team of individuals with strong scientific backgrounds and a high degree of knowledge in the products and disease area at stake.

Servier thus queried the evidentiary basis and reasoning for the Panel's ruling that its activities breached Clauses 2, 3.2, 9.1 and 15.2 of the Code. These rulings appeared to be disproportionate and compromised legal certainty to the detriment of Servier's operation.

Servier submitted that the purpose of the MLS cardiovascular team was to address spontaneous enquiries about Procoralan which was why 'Answer medical enquiries' was listed as one of the principal responsibilities in the relevant job description. Procoralan was already licensed and marketed for angina, hence Servier received enquiries about a number of different aspects of the product, including safety, use by the elderly, use in heart failure, arrhythmias or acute coronary syndrome. Depending on the specific enquiry therefore, both on- and off-licence topics might be covered.

In developing the MLS role, Servier submitted that it had relied on the relevant sections of the Code concerning the provision/exchange of non-promotional scientific information, as well as previous rulings. Indeed, the Code made specific provision for factual responses to unsolicited enquiries (supplementary information to Clause 1.2), the legitimate exchange of medical and scientific information (supplementary information to Clause 3), advanced budgetary notification (supplementary information to Clause 3.1) and the maintenance of a scientific service (Clause 21). Against this background, Servier had relied on the Panel's ruling in Case AUTH/1910/11/06 that it was 'not necessarily unacceptable for companies to have employees focussing on the provision of information prior to the grant of the marketing authorization', provided that the arrangements and activities were carefully controlled and managed. Indeed, this decision was duly noted in one of the MLS training presentations approved by Servier ('ABPI Code Update: Focus on Field Based Medical Information – August 2008').

Further, the MLS role was developed in line with the practices of the industry as a whole: companies commonly maintained a field-based medical and scientific liaison team, a role which had evolved considerably in recent years. Indeed, the first Medical Science Liaison (MSL) conference to be held in the UK took place in 2010 ('The European MSL and Medical/Scientific Advisor Best Practices Conference', run by ExL Pharma). Servier provided a selection of the speaker presentations and noted that, compared with some pharmaceutical companies, it had taken a relatively conservative approach to the scope of the role; for example, one presentation described a very active MSL team with 2000 pre-licence discussions over an 8 month period for one product and an unprecedented

number of stakeholder comments for a National Institute for Health and Clinical Excellence (NICE) single technology appraisal for another product being attributed to the activity of the team. Further, the presentations also highlighted the value of the MSL role to the NHS. One presentation helpfully explained how a field-based MSL team could bring medical value to customers, including through publications, medical information, advisory boards and scientific updates. Servier also provided a company's job advertisement for an MSL role, from which it was clear that there was a proactive component pre-licence. Again, this illustrated Servier's conservatism compared with prevailing industry practice. The content of the MSL conference, together with the job description, supported the conclusion that the industry as a whole had understood the ruling in Case AUTH/1910/11/06 as a confirmatory signal for maintaining a field-based MSL team, an interpretation which was consistent with the provision made in the Code for the provision/exchange of non-promotional scientific information (Clauses 1.2, 3 and 21 as cited above).

Servier knew that its MLS role, which benefitted the NHS, also brought challenges due to the need to ensure that information with regard to unlicensed usage was strictly controlled. In developing the MLS role, Servier had thus ensured robust procedures, documentation, instructions and training.

Servier noted that its MLS team had no remit, mandate or incentive to promote any products (including licensed products). The team's main responsibility was to address spontaneous enquiries about Procoralan (ie the emphasis of the role was reactive in nature), as stated in the relevant job description. Secondary to that, and on a limited basis, other activities included management of non-interventional studies, delivery of medical and educational goods and services, training of other Servier staff, the non-promotional exchange of medical and scientific information (including involvement in advisory boards) and, to a small extent, advanced budgetary notification. In practice, the non-promotional role of the MLS team was achieved through the company structure, as well as rigorous training and robust policies.

With regard to the company structure, Servier noted that it did not mix promotional and non-promotional roles; the MLS team and the key account managers (KAMs, the only Servier employees with a selling remit) thus had completely separate reporting lines up to the chief executive officer, in each case with two levels of management between. The company organogram was provided. The MLS team reported to the national cardiovascular medical liaison manager, who in turn reported to the director of medical affairs. The KAMs, however, reported to their relevant therapy area divisional healthcare development manager each of whom reported to the director of healthcare development (the role closest to that of a national sales manager). This ensured that there was no overlap between the MLS role and KAM role. Servier submitted the respective job descriptions showed that the roles were entirely distinct. MLSs were not selected on the basis of their selling abilities but primarily for their medical/scientific knowledge and ability to communicate that knowledge (reference was made to the 'Indispensable Qualities' listed in the MLS (Cardiovascular) Job Description). In contrast, KAMs were selected on the basis of their selling ability, hence one of the indispensable qualities was to be 'Commercially astute and passionate about delivering results'.

Servier submitted that because the MLS role did not merge promotional and non-promotional functions, none of the material provided to the MLS team was promotional in nature. The Panel referred to three powerpoint presentations which were provided to the MLS team on request of medical enquiries: 'Ivabradine in Heart Failure'; 'Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial' and 'SHIFT-PRO Quality of Life Substudy'. Unfortunately, human error by an administrator which was not picked up by the signatories concerned, led to the first of these presentations being wrongly certified on a form intended for the certification of promotional items. In fact, the content was entirely non-promotional and should have been certified as such, consistent with the other two presentations; this error had now been rectified.

Servier had rigorous training procedures in place to ensure that the MLS team acted within the scope of its duties. Servier referred to the presentation 'Training on Advanced Budgetary Notification from National CV Medical Liaison Manager' as well as the relevant training and briefing materials. In particular, Servier referred to one of its MLS training presentations, a Code update which focussed on field-based medical information, which summarised the wide-ranging and important functions undertaken by the MLS team, from providing medical information in response to unsolicited enquiries to the organisation of advisory boards. The fundamental message of the presentation was that the MLS role was strictly non-promotional and therefore, whatever the task undertaken, it was critically important that the MLS team did not promote Servier's products. Servier submitted that the principles outlined in the presentation were upheld in the sound policies and procedures on which its MLS team was founded, and which were reflected in the operation of the team.

Servier submitted that advanced budgetary notification was a small but predetermined part of the MLS role and in-house data showed that advanced budgetary notification for ivabradine in heart failure had been very limited. Out of 116 advanced budgetary notification letters sent nationally since the SHIFT study results were published in September 2010, there had been 12 responses declining or deferring a meeting, and 36

requests for a meeting (which were indeed followed up by a meeting in each case) (January – June 2011). There were additionally 37 other requests for budget impact or cost effectiveness information arising spontaneously. Servier noted that the MLS team did not have any targets to meet in relation to advanced budgetary notification correspondence.

Servier submitted that the advanced budgetary notification material had been certified, which demonstrated that the company was concerned to ensure that communication regarding unlicensed usage was strictly controlled. The presentations demonstrating 'Cost effectiveness analysis of ivabradine in heart failure in a UK setting' and the 'Budget Impact Model based on results of SHIFT study' had been correctly certified as non-promotional, albeit only as a response following an unsolicited request. In its ruling, the Panel queried whether these materials constituted the data and modelling tools which the MLS in question had proactively offered; the answer was yes – Servier believed that these materials might be legitimately proactively disseminated in the context of advanced budgetary notification and should have been certified as such. This error had now been rectified.

Servier noted that with regard to its advanced budgetary notification procedure, the Panel queried whether the information about the product had been supplied early enough such that budget holders etc could be reasonably expected to act upon it. Servier noted that the supplementary information to Clause 3 of the Code stated: 'Health authorities and health boards and their equivalents, trust hospitals and primary care trusts and groups need to estimate their likely budgets **two to three years in advance** in order to meet Treasury requirements and there is a need for them to receive advance information about the introduction of new medicines, or changes to existing medicines, which may significantly affect their level of expenditure **during future years**' [emphasis added]. In spite of this wording, the current fundamental transformation within the NHS could not be ignored. Indeed, the structures explicitly referred to within the supplementary information to Clause 3.1 were being phased out, and corresponding revisions to the Code would be required. In Servier's view it was crucial for the industry to respond to the NHS need for budgetary information at the appropriate time; this was surely the purpose of the provisions on advanced budgetary notification. Only providing the information two to three years in advance, as referred to in the Code, did not meet the 'modern' needs of the NHS. By way of illustration, Servier referred to an ABPI email dated 29 July 2011 addressed to UK PharmaScan Champion Users which stated: 'You will probably be aware that the NHS financial planning cycle which determines budgetary spend for the year April 2012 – March 2013 will begin in September/October 2011. We have been given feedback from the NHS that current financial pressures mean that this timeline will be more important than ever this year for those in the NHS managing the entry of new medicines'. It therefore appeared that NHS financial planning cycle operated approximately 6-18 months in advance of budgetary spend. The heart failure indication for Procoralan originally expected in October/December 2011 or January/March 2012 was now anticipated in April/June 2012. Accordingly, Servier contended that by providing information to those responsible for making policy decisions on budgets between 15 months and even up to 6 months before the anticipated launch of Procoralan (on the basis of the original timeline forecast), the company had best fulfilled the function of advanced budgetary notification, ie to assist budget holders to determine budgetary spend. Accordingly, in answer to the Panel's query as to whether the information had been supplied early enough such that budget holders could be reasonably expected to act upon it, Servier believed that it had and reflected a proper partnership with the current, evolving NHS.

Servier noted that the Panel also queried whether the introduction of Procoralan for chronic heart failure would have a significant budgetary implication. Servier noted that significant was not defined in the Code; currently, NHS managers were experiencing a budget squeeze without precedent, and were perhaps themselves best placed to evaluate significance. Servier developed its advanced budgetary notification procedure in good faith, mindful of the current economic pressure on the NHS, and in the belief that the relevant budgetary impact estimates might be considered significant by NHS managers. Whilst Servier acknowledged that no details were provided in the access letter on the budgetary implication, Servier's budget impact model based on the results of SHIFT study showed a typical net annual cost of treating with ivabradine of £3,000-£9,000 per 100,000 head of population. The fact that half of all budgetary information calls were in response to spontaneous enquiries (37/73) strongly indicated that the NHS considered that spend on products/indications such as the one at issue to be significant.

Servier denied that it had promoted Procoralan for the unlicensed indication of heart failure.

Servier understood the Panel to have ruled of a breach of Clause 3.2 because the Panel considered that:

- Servier's advanced budgetary notification procedures did not meet the conditions set out in the supplementary information to the Code; and therefore
- Servier had 'arranged for its staff to proactively call upon health professionals and others to raise awareness of the use of Procoralan for an unlicensed indication';
  and therefore
- Servier's activities amounted to the promotion of Procoralan for an unlicensed indication.

Servier submitted that its advanced budgetary notification procedures complied with the Code.

However, even recognising that these procedures could be improved to provide specific information about the budgetary implications of the forthcoming indication in the access letter (a point which had emerged only as a result of the incident at issue and the company's review of the Panel's ruling, as well as the recent conclusion of Case AUTH/2327/6/10, but not previously obvious), Servier did not accept that its activities amounted to the promotion of Procoralan. The access letter included only factual information and it was clear that the purpose of the contact was to provide those who had a role in policy making or determining budgets with 'the relevant clinical and budgetary data relating to this product to assist your planning process'. Servier noted that legitimate targets for advanced budgetary notification were policy makers (who were often clinicians) and budget holders (often medicines management pharmacists). Again, the company's advanced budgetary notification procedure was designed in good faith, based on its understanding of the needs of the NHS, rational interpretation of the Code, previous rulings and the prevailing industry practice.

Servier disputed that it 'arranged for its staff to proactively call upon health professionals and others to raise awareness of the use of Procoralan for an unlicensed indication'. The Panel cited in evidence of this the fact that, in the last 6 months, the MLS in question had contacted 57 health professionals/budget holders about the use of ivabradine in heart failure. Fifty-seven contacts over a 6 month period would be very few indeed if Servier had, in fact, implemented a proactive, promotional communication programme as the Panel implied. Further, the Panel had wrongly assumed that the contacts in question were all proactive or related to advanced budgetary notification; this was not the case. Indeed, the majority of the work of the MLS team consisted of responding to unsolicited enquiries, with limited other types of contact. Servier considered that the Panel was misleading in its summary of the general guidance about responding to spontaneous enquiries about heart failure; it had implied that the guidance to KAMs referred only to one option in the event of enquiries on the SHIFT study: 'Key account managers were then instructed to say that they could not discuss this further but should further information be required the preferred option for follow-up was for a cardiovascular MLS to arrange a meeting'. However, the guidance actually showed that there were three options: a meeting with the MLS (cardiovascular), a phone-call from a scientific and medical information advisor or a meeting/phone-call with a medical advisor.

Servier noted that the Panel had stated that: 'The proactive provision of information by a pharmaceutical company about the unauthorized use of a medicine was very likely to be seen as promotion'. However, the majority of MLS contacts were reactive, and further, it could not be assumed that proactive contact about unlicensed indications was always promotional; this was why the supplementary information to Clause 3 specifically provided that medical and scientific information could be exchanged during the development of a medicine and that advanced budgetary notification might be performed. If all exchange was limited to responding to unsolicited enquiries then the supplementary information to Clause 3 would be redundant (Clause 1.2 stated that factual replies in response to unsolicited enquires were outside the scope of promotion).

Given the above, Servier strongly disputed that it had promoted Procoralan for an unlicensed indication. The Panel's conclusion did not correspond to the evidence and appeared to have been reached through a series of assumptions. The ruling provided no certainty for the company, which was of great concern to Servier in terms of the everyday operation of the MLS team.

Servier submitted that the Panel's ruling of a breach of Clauses 9.1 and 2 followed on from its conclusion that Servier had promoted Procoralan for an unlicensed indication. As Servier disputed the Panel's ruling of a breach of Clause 3.2, it also disputed the Panel's ruling of a breach of Clauses 9.1 and 2.

More specifically, with regard to Clause 9.1, Servier submitted that it had maintained high standards. These high standards were reflected in its policies relating to the role and activities of the MLS team, as well as its training material. In particular, whilst Servier recognised that its advanced budgetary notification procedures could be further tightened in light of the Panel's comments, it did not agree that it had failed to maintain high standards and considered that its interpretation of Clause 3 was reasonable in light of prevailing industry norms.

Servier was very concerned that the Panel had ruled a breach of Clause 2 of the Code, which should be reserved as a sign of particular censure. In Servier's view the Panel had based its conclusion of off-licence promotion on a series of assumptions triggered from an isolated and regrettable incident concerning one MLS, rather than on the evidence before it. The Panel stated that it 'considered that the activity amounted to a softening of the market for using Procoralan in heart failure'; but it did not specify what activity it was referring to (whether the advanced budgetary notification activity or other conjectured activity of the MLS team). If the Panel objected to the fact that Servier's access letter did not state the budgetary implications of the forthcoming heart failure indication, then the ruling of a breach of Clause 2 was disproportionate. Servier submitted that its advanced budgetary notification procedure was designed in good faith, based on the company's rational interpretation of the Code, previous Panel rulings and the prevailing industry practice. Accordingly, Servier did not believe that it has brought discredit upon, or reduced confidence in, the pharmaceutical industry.

As the MLS team did not have a promotional role,

either in principle or in practice Servier had appealed the ruling of a breach of Clause 15.2, which referred to the conduct of 'representatives'. Servier's MLS team did not fall within the definition of 'representatives', as they were not 'calling on members of the health professions and administrative staff in relation to the promotion of medicines' (Clause 1.6). Specifically, the MLS concerned did not call on health professionals to promote Procoralan for heart failure; he approached them within the framework of advanced budgetary notification, albeit clumsily, as detailed above.

Whilst Servier recognised that the emails at issue did not represent the high standards of Servier and were apparently misinterpreted, it did not accept that the correspondence amounted to the promotion of Procoralan for heart failure, or that this conclusion might be reached from the evidence. Servier submitted that the pre-licence context, the non-promotional role of the MLS and a sense of future planning were consistent in the communication thread. Engagement with the health professionals at issue was clearly in their respective roles of policy maker and budget holder. The purpose of the communication was to obtain information on appropriate contacts in order to approach them in respect of advanced notification of ivabradine for heart failure, as evidenced by the written statement from the MLS concerned (a copy was provided). The MLS concerned was referred to each contact by the preceding one, commencing with the chief executive officer. Servier noted that the email title 'Ivabradine in heart failure' was not written by the MLS, but added by one of the contacted health professionals who unfortunately jumped to the conclusion that the email thread was promotional, which did not appear reasonable in the context, and particularly given that the MLS stated up-front that he was not part of the sales force and had clearly entered into the correspondence in good faith. Servier therefore considered that the Panel's ruling of a breach of Clause 3.2 was disproportionate.

Servier submitted that this case has taught it that, even with robust procedures and training, unfortunate incidents might occur. Servier fully stood by the important role played by its MLS team, as testified by its commitment to strengthen yet further its policies and procedures relating to the MLS team. To this end, Servier had:

- In good faith suspended advanced budgetary notification, pending the outcome of the appeal;
- Amended human errors of certification and appropriately briefed all Servier staff and contractors concerned with Code compliance and
- Introduced a new requirement that all MLS emails to health professionals (including those in commissioning groups) were copied to the national MLS manager. These new processes were intended to ensure standardised communication and support compliance.

For the reasons explained above, Servier appealed the Panel's rulings of breaches of Clauses 2, 3.2, 9.1 and 15.2 relating to the activities of the company, as well as Clause 3.2 relating to the activities of the individual MLS concerned.

COMMENTS FROM THE COMPLAINANT

The complainant considered that his original comments stood. The offer of 'pathway development' in heart failure was a way in to discuss the findings of the SHIFT study and therefore get commissioners interested in using an unlicensed and contraindicated medicine in heart failure.

APPEAL BOARD RULING

The Appeal Board noted that Clause 3 prohibited promotion of a medicine prior to the grant of its marketing authorization and also required that promotion of a medicine was in accordance with the terms of its marketing authorization and not inconsistent with its SPC. The supplementary information to Clause 3 set out guidance in relation to certain situations including the provision of advanced notification of new products or product changes. This supplementary information included a requirement that such information must include the likely cost and budgetary implications and this must be such as to make a significant difference to the likely expenditure of health authorities, trusts and the like.

The Appeal Board noted that the emails at issue sent by the MLS did not discuss the anticipated cost or the budgetary implications of using Procoralan for heart failure. The Appeal Board noted that one of the MLS's emails stated that 'I have seen many consultant cardiologists in the [local] region and the responses have been very positive. In some areas clinicians are already using the product (off licence) in heart failure. As a consequence I felt it appropriate to make contact, to ensure that as the director of clinical transformation, you would have an opportunity to be brought up to date with the most recent data that we have'. The Appeal Board considered that the very positive description of the heart failure indication in the absence of any discussion either of the budgetary implications or the significance of the difference in expenditure meant that the MLS had promoted Procoralan for an unlicensed indication. The email in question could not take the benefit of the exemption for advance notification set out in the supplementary information to Clause 3.1. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

The Appeal Board noted that 'representative' was defined in Clause 1.6 of the Code as 'a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines.' It considered that its ruling that the product had been promoted for an unlicensed indication did not mean that it considered that the MLS job description described a representative's role as defined in Clause 1.6. The

Appeal Board thus ruled no breach of Clause 15.2 as this clause applied to the conduct of representatives. The appeal on this point was successful.

The Appeal Board noted that advanced information about an unlicensed indication could only be supplied if such use of the product had a significant budgetary implication and the information included details of the likely cost and budgetary implication. The relevant supplementary information to Clause 3.1 set out detailed conditions. The Appeal Board noted Servier's submission for the appeal that its Budget Impact Model, based on the results of the SHIFT study (Swedburg *et al*), showed a typical net annual cost of treating heart failure with Procoralan of £3,000-£9,000 per 100,000 head of population. The Appeal Board noted in the email correspondence the head of prescribing and medicines management stated that the estimated cost to the PCT of using Procoralan in a suitable population was around £75,000/year but there would be 'therapeutic creep' and so the cost would be considerably more. The head of prescribing and medicines management also stated that the patients in the study were not on optimum doses of beta-blocker. The Appeal Board considered that NHS managers were likely to regard such potential increases in budgetary requirements as significant. This was particularly so given the current economic environment. The Appeal Board considered that the licence extension application for Procoralan for heart failure satisfied the condition in the supplementary information to Clause 3.1 that advanced notification information might be provided for '… a product which is to have a significant addition to the existing range of authorized indications …'.

The Appeal Board did not consider that starting the advanced notification in August/September 2010 for changes to the licence expected by the end of 2011 was unacceptable. The Appeal Board noted Servier's submission for the appeal that the licence was now expected in April/June 2012. The Appeal Board noted the access letter discussed the ivabradine licence application to add an indication for chronic heart failure. The letter detailed the current licensed indication and stated that the Code advised that advanced budgetary information might be provided to policy influencers and those responsible for budgetary decisions to aid future planning. The Appeal Board considered that the purpose of the letter was to determine if recipients were responsible for budgetary decisions and if so to provide '…the relevant clinical and budgetary data relating to this product to assist your planning process'. The letter also stated that the author intended to contact the recipient to organise a meeting. Servier submitted that from the 116 letters sent there had been 36 requests for a meeting and another 37 meeting requests had arisen spontaneously.

The Appeal Board considered that advanced notification was a difficult area and care was needed to satisfy the relevant requirements of the supplementary information to Clause 3.1. The Appeal Board was concerned about some of the claims made in material used by the MLSs and also about their proactive contact of key opinion leaders. Nonetheless the Appeal Board did not consider that the company's activity amounted to the promotion of Procoralan for an unlicensed indication. The Appeal Board also noted that the complainant had emphasised the role of the individual MLS as evidenced by the email trail rather than activities undertaken by the company. The Appeal Board ruled no breach of Clause 3.2. The appeal on this point was successful.

The Appeal Board noted the rulings of a breach of the Code in relation to the MLS in question. The Appeal Board considered that Servier should have more closely controlled its MLS team. High standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

During its consideration of this point the Appeal Board noted Servier's recent decision that emails sent by the MLS team be copied to their manager but queried whether this on its own introduced sufficient control.

The Appeal Board noted its rulings above and thus considered that this case did not warrant a ruling of a breach of Clause 2 and no breach of that clause was ruled. The appeal on this point was successful.

Given its rulings the Appeal Board decided to take no further action in relation to the Panel's report made in accordance with Paragraph 8.2 of the Constitution and Procedure.

Complaint received **14 June 2011**

Case completed **10 October 2011**