CASE AUTH/2327/6/10

MHRA v GRÜNENTHAL

Promotion of tapentadol

The Medicines and Healthcare products Regulatory Agency (MHRA) advised the Authority that it was concerned that Grünenthal was promoting its unlicensed medicine, tapentadol, to health professionals. The matter was taken up as a complaint under the Code.

The MHRA explained that it had received an allegation that suggested that Grünenthal had promoted its unlicensed product, tapentadol, to health professionals. The MHRA knew from previous correspondence with the company that its team of health economic liaison managers (HELMs) contacted 3,000 health professionals about the product's budgetary implications in advance of the grant of a marketing authorization. The MHRA deemed this activity to be promotional and provided advice on compliance with the law. A report of the case was provided.

The anonymous source alleged that the company had continued to target health professionals and it set call rates for this and had supporting materials, including slides, to use in proactive discussions with NHS staff.

The MHRA would take a very serious view of any further promotion of tapentadol in advance of the grant of a marketing authorization since Grünenthal had already been censured by the MHRA for the previous case. In addition the MHRA had asked to vet all promotional and related materials for the product, including any proactive materials for use by HELMs.

In the absence of any evidence of actual promotion from a recipient, the MHRA did not consider it appropriate to take forward a legal investigation for breach of the regulations. Instead it asked the Authority to investigate Grünenthal's actions to ensure that it had not promoted tapentadol and that it had appropriate procedures and controls in place for its HELMs and any other staff that might discuss unlicensed medicines with health professionals.

The detailed response from Grünenthal is given below.

The Panel noted that the complaint from an anonymous source to the MHRA was that Grünenthal continued to promote tapentadol prior to the grant of a marketing authorization. The MHRA had received a complaint about the matter in November 2009 and had agreed action with Grünenthal in January 2010. The Panel noted that the MHRA had considered the activities in relation to the Advertising Regulations and the Blue Guide. The Panel considered that it was limited to considering Grünenthal's activities after January 2010 in relation to the Code.

The Panel noted Grünenthal's comments about the anonymous source of the complaint to the MHRA and the burden of proof. The Panel noted, as set out in the introduction to the Constitution and Procedure, that complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties.

The Panel noted that Grünenthal had begun an advance notification process for tapentadol in November 2009 ie only 10 months before it anticipated having a marketing authorization for the medicine. 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. Information could only be supplied if the product had a significant budgetary implication. The Panel queried whether this was so but did not consider this was relevant to the complaint before it.

It appeared, that, in compliance with a request from the MHRA, that whilst HELMs were not given any printed material regarding tapentadol, they could still talk about it. The Panel considered that this approach was wholly unacceptable. The HELMS were given, inter alia, information about tapentadol some of which was headed 'not approved for distribution'. Some of this material showed an advantage for tapentadol vs oxycodone. In the Panel's view, the more information the HELMs were given about tapentadol the more likely they were to use it with their customers for commercial advantage.

The Panel noted Grünenthal's submission that the HELMs had not engaged in any proactive advance notification for tapentadol following an agreement with the MHRA in January. It appeared that since then the HELMs had undertaken a formulary mapping exercise to gain an understanding of how a new medicine would be introduced into the local health economy. This exercise required the HELMs to seek answers to a number of key business questions. Some of those questions were detailed in a briefing presentation, 2 March, and included the following: 'Identify attitudes to [controlled drugs] and tapentadol in nociceptive neuropathic and specifically back pain'; 'Where do they see tapentadol on the analgesic ladder?'; 'Where does the customer see a new pain drug adding most value?' and 'Does [drug and therapeutics] need to be achieved before a new pain drug can be used?'. The Panel noted Grünenthal's submission that following dialogue with the MHRA in April 2010, HELMs were briefed to discuss the process issues in relation to new products in general. Further formulary mapping questions appeared in a presentation dated 28 April 2010.

The Panel noted that the HELMs visited individuals responsible for the approval and purchase of medicines within the NHS; they also visited those who had to gain approval for the use of medicines in local health economies. The HELMs proactively saw both types of customers in relation to Grünenthal's licensed products all of which were for pain relief. The Panel considered that in this regard customers would see the HELMs as medical representatives. To have that same group of people then asking questions about tapentadol or a 'new pain drug' would be seen as promotional.

The Panel disagreed with Grünenthal's submission that the HELM position was a non-promotional role. Their activities were not limited to a fact finding role as the nature of the questions they were to ask would raise interest and awareness in the new product and solicit questions about it. The slides presented to the HELMs about tapentadol reinforced the promotional aspect of their activity. The HELMs were expected to have selling skills and they visited the same people to tell them about licensed medicines and to ask them questions about tapentadol and/or 'a new pain drug'. In the Panel's view asking such questions amounted to the promotion of tapentadol before the grant of its marketing authorization. Thus a breach of the Code was ruled. The Panel considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel considered that to brief a team, employed for its selling skills, to raise the profile of tapentadol and/or 'a new pain drug' just weeks before the expected grant of a marketing authorization was unacceptable. The Panel was very concerned about the failure to provide the HELMs with clear written instruction and this was a particularly serious omission given the concerns raised by the MHRA about the activity. The Panel considered that the activity amounted to a softening of the market. Such activity brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of the Code was ruled.

The Panel was extremely concerned about Grünenthal's activities with regard to the advanced notification of tapentadol. The MHRA had provided advice to the company following a mailing about tapentadol to 3,000 people. Since being in correspondence with the MHRA, Grünenthal had used a team of HELMs to gather information about, inter alia, attitudes to tapentadol and how to get 'a new pain drug' on to a formulary. The HELMs were expected to have selling skills and saw some of the same people about licensed and unlicensed medicines. The HELMs were expected to work closely with the sales team. Briefings to HELMs about this matter after the intervention of the MHRA were inadequate. Overall the Panel considered that Grünenthal's activity amounted to the promotion of tapentadol prior to the grant of its licence. In the Panel's view the HELMs' activities did not constitute the advance notification of tapentadol as no information was being supplied that showed that the product would have a significant budgetary effect. The Panel considered that overall Grünenthal's actions were unacceptable. 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. The Panel noted Grünenthal's submission that on receipt of this complaint it had suspended all formulary mapping activities.

The Appeal Board noted from the company representatives that Grünenthal had originally set up a market access team to try to limit the extensive off-label use of Versatis and to gain market access for its portfolio of licensed pain medicines. Part of the HELMs' role was to promote Grünenthal's medicines. The company had then used this same team, with the same job description, to work on the advance notification of tapentadol. The Appeal Board was very concerned about the conduct of Grünenthal. The prohibition on the promotion of a medicine prior to the receipt of its marketing authorization should have been well understood. It appeared that Grünenthal had not taken the opportunity to thoroughly review the HELMs' role and responsibilities when the MHRA had determined that, in providing advance notification, they had infact promoted tapentadol prior to the grant of its marketing authorization. Although changes had been made to the way the HELMs worked at this point, in that they had no role in relation to advance notification, the account mapping and other activities which they carried out were considered by the Panel to still amount to the promotion of a medicine prior to the grant of its marketing authorization. This was unacceptable.

The Appeal Board was very concerned to learn that the market access team had generated presentations and briefing materials for the HELMs which had not been certified. In that regard the Appeal Board queried whether the senior management team had exercised sufficient control over the market access team especially considering it was newly appointed, had responsibilities for an unlicensed medicine and the MHRA's involvement in the matter.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of Grünenthal's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted as soon as possible. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the audit report (October 2010) the Appeal Board noted that Grünenthal had agreed compliance plans which would address all the areas recommended for attention and this was already being implemented.

The Appeal Board decided that a second audit should be carried out in February 2011 when it would expect the recommendations in the audit report to be implemented. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the second audit report (delayed until March 2011) the Appeal Board was encouraged by Grünenthal's progress since October but considered that the company still needed to demonstrate that it understood the importance of compliance. The Code and its requirements needed to become embedded into all levels of the company.

The Appeal Board decided that a third audit should be carried out in September when it would expect the recommendations in the audit report to be implemented. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon consideration of the third audit the Appeal Board was concerned that it still appeared that the company had not really understood the seriousness of the situation. The Appeal Board was extremely concerned to note errors in the response from Grünenthal to the recommendations from the March 2011 audit (part of the preparation for the September 2011 audit). This was unacceptable. It was hard to believe, given the recommendation in March that the company should be confident that all the Versatis material was clear regarding the licensed indication, that the company had not been precise about what had been done. Senior employees had not taken decisive action to implement the recommendation. The failure of senior employees to respond in full to questions at the audit about that recommendation led the Appeal Board to question the company's stated commitment to compliance.

The Appeal Board decided that Grünenthal should be publicly reprimanded in relation to the misinformation in its response to the Authority. Prior to the third audit the Appeal Board was extremely concerned about the apparent lack of demonstrated change in the company culture. It noted that some activities had been started and these might improve the situation. A new general manager was appointed in October. The Appeal Board decided that a fourth audit of Grünenthal should take place by mid February 2012. Upon receipt of the report for that audit, it would decide whether further action was needed.

Upon consideration of the forth audit report (February 2012) the Appeal Board noted that Grünenthal had undergone changes in senior staff including a new general manager. There appeared to be a different culture in the company and a more positive attitude to compliance. The Appeal Board considered that there had been encouraging progress since the last audit. On the basis that the company adopted an approach of continual improvement the Appeal Board considered that no further action was required.

The Medicines and Healthcare products Regulatory Agency (MHRA) advised the Authority that it was concerned that Grünenthal was promoting its unlicensed medicine, tapentadol, to health professionals. The matter was taken up as a complaint under the Code.

Tapentadol had a combined mechanism of action, mu-opioid-receptor agonism (MOR) and noradrenaline reuptake inhibition (NRI).

COMPLAINT

The MHRA explained that it had received an allegation that suggested that Grünenthal had promoted its unlicensed product, tapentadol, to health professionals. The MHRA knew from previous correspondence with the company that its team of health economic liaison managers (HELMs) contacted 3,000 health professionals about the product's budgetary implications in advance of the grant of a marketing authorization. The MHRA deemed this activity to be promotional and provided advice on compliance with the law. A report of the case was provided.

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The MHRA would take a very serious view of any further promotion of tapentadol in advance of the grant of a marketing authorization since Grünenthal had already been censured by the MHRA for the previous case. In addition the MHRA had asked to vet all promotional and related materials for the product, including any proactive materials for use by HELMs.

In the absence of any evidence of actual promotion from a recipient, the MHRA did not consider it appropriate to take forward a legal investigation for breach of the regulations. Rather the MHRA asked the Authority to investigate Grünenthal's actions to ensure that it had not promoted tapentadol and that it had appropriate procedures and controls in place for its HELMs and any other staff that might discuss unlicensed medicines with health professionals.

When writing to Grünenthal, the Authority asked it to respond in relation to Clauses 2, 3.1 and 9.1 of the Code.

RESPONSE

Grünenthal submitted that it took this matter very seriously and was undertaking a thorough investigation into the anonymous, unsubstantiated allegation forwarded from the MHRA that 'the company had continued to target health professionals and it set call rates for this and had supporting materials, including slide sets, to use in proactive discussions with NHS staff'. Grünenthal concluded that the allegation was without merit.

Grünenthal noted that the Code allowed for advanced notification of products (in accordance with Clause 3.1) so that NHS budget holders and those with policy influence could forward plan for products to be introduced where such products might have a significant budgetary impact.

Grünenthal anticipated that tapentadol (trade name Palexia) would receive UK marketing authorization in September 2010 and that it would have a significant budgetary impact on the NHS. The reasons for the significant budgetary impact were as set out in a document compiled in discussion with the MHRA but never used. A copy of the document was provided. As NHS budget holders and policy makers might often need a considerable lead time to plan, Grünenthal began an advance notification process, including a certified letter sent in November 2009, the intention being to send that letter to a small number of such budget holders/policy makers. The letter to identified budget holders/policy makers set out a limited set of facts about tapentadol (which in Grünenthal's view was in line with Clause 3.1 supplementary information) and offered a HELM to visit to discuss the details of the budgetary impact.

Grünenthal submitted that a complaint (anonymised to Grünenthal) was received by the MHRA in November 2009. The MHRA contacted Grünenthal on 26 November concerned that the advance notification letter that Grünenthal had sent out did not comply with Section 4.2 of the MHRA's Blue Guide and that the HELM visit being offered was promotional in nature. Grünenthal wrote to the MHRA on 1 December to confirm that further dissemination of this letter and similar materials, as well as meetings, had been suspended pending resolution of the case.

Grünenthal discovered that the letter had been sent by one of its employees to approximately 3,000 people, some of whom had responsibilities that were not primarily related to budgets or policy making. Grünenthal took this matter very seriously, admitted the error and apologised to the MHRA. Grünenthal agreed to make no further use of the letter and to implement processes to check all future distribution lists of mailings. That matter concluded with a summary report published by the MHRA on 11 March 2010. Grünenthal considered the matter closed and had had no further contact with the MHRA on this matter.

With the continuing desire to fully comply with all applicable rules Grünenthal sought clarification from the MHRA about exactly what materials the MHRA needed in respect of advance notification in order to review how it could proceed with this business process. Grünenthal put forward proposals on how it might go about the advance notification process and how it might confirm the exact identity and ascertain the specific interest of named budget holders/policy makers and offer a meeting with a HELM. Two draft briefing documents were rejected by the MHRA and therefore had never been used (copies were provided).

More generally, Grünenthal submitted that it had a number of processes in place to address the MHRA's concerns and to comply with the rules:

- Medical information routinely handled tapentadol enquiries; all enquiries went to medical information for review. Only on a specific request would tapentadol information be given out by medical information, and all such requests were recorded and tracked in a medical tracking system (MedInfoSys).
- All field staff had been briefed on how to handle all enquiries (including tapentadol) so as to route these through a written 'request for information' from health professionals or appropriate administrative staff and signed by those health professionals or appropriate administrative staff. Grünenthal provided certified briefing materials. All requests for information were recorded and tracked in MedInfoSys.
- Upon request from the MHRA, a specific request for information system for budget holders/policy maker enquiries was established. Prior to this the existing request for information system was in place at all times.
- During enquiries related to collecting information on formulary systems and protocols for new medicines, some budget holders/policy makers requested specific budgetary information about tapentadol from a HELM. The appropriate medical information response was clearly outlined in the briefing to the HELM team on the 28 April 2010 (provided) after obtaining final clarification with the MHRA.
- The MHRA also required that all other tapentadol advertising and promotional materials related to tapentadol should be reviewed by the MHRA before use. Grünenthal had agreed to this.

Grünenthal provided a copy of the HELM job description and submitted that essentially, this was a non-promotional role to help budget holders/policy makers plan for the inclusion of Grünenthal products within their locality. Grünenthal also provided the briefing instructions for the HELMs, which it submitted emphasized the importance of not proactively raising tapentadol: -

a) 4 February 2010 – 1st Joint Health Economic Liaison Managers Meeting – another pharmaceutical company/Grünenthal. By way of an explanation:
   i) Slide 38 referred to MOR-NRI (the mode of action of tapentadol). The verbal briefing referred to post licence work as this slide set covered all strategic and tactical elements of the launch programme. No HELM pre-launch MOR-NRI materials were approved for use.
   ii) Slide 43 referred to 'Raise awareness of Palexia' – this was part of the post licence strategy and clearly a critical success factor in its commercialization.
   iii) Slide 69 set out annual contacts related to account mapping with payers. This was not related to MOR-NRI or product but looked at cost containment in pain related matters. Grünenthal focused on pain management.
   iv) Slide 82 referred to HELM clinical contacts. HELM did not meet clinicians per se but some budget holders/policy makers had clinical attachments. HELMs were instructed that where a clinical question arose, to raise a request for information, which could lead to a medical science liaison (MSL) visit if the clinician so wished.

b) 2 March 2010 – 2nd Joint Health Economic Liaison Mangers Meeting – another pharmaceutical company/Grünenthal (documents provided). An advanced notification documentation in draft form was reviewed but never used – slides were attached. Key business question 1 (KBQ1) referred to ladders of adoption as part of the 'Tapentadol Road Map' - aimed at identifying accounts and processes for formulary applications.

c) Grünenthal was in an ongoing dialogue with the MHRA from January 2010. This finally resulted in a meeting with the MHRA on 31 March 2010. A HELM briefing meeting (documents provided) was subsequently held on 28 April 2010, which was consistent with the final MHRA letter dated 29 April 2010.

   The slides 'Palexia Market Access Plan' (provided) covered the current HELM activity with timelines for tapentadol activity (text in red) after the anticipated marketing authorization date in September (slides 14,15) and contingencies to adjust dates should the marketing authorization dates change (slide 16).

   The slides 'Materials' (provided) looked at Versatis cost-efficacy considerations, and account mapping. HELMs were directed to send a request for information to medical information in the event that questions were asked about any products. The request must be specific about the product in order that medical information could answer specifically.

d) Belfast company meeting - (documents provided)

e) Request for information, May HELM briefing – (documents provided)

Grünenthal' submitted that HELMs were trained to undertake account mapping for the future formulary inclusion of tapentadol. This was outlined in a series of briefing presentations to the HELM team (see above) as to how they should engage with customers. Following Grünenthal's final dialogue with the MHRA in April 2010, its brief from the ruling was to engage with budget holders/policy makers only to establish the process by which new products in general might be submitted for local drug and therapeutic committee review.

Grünenthal' stated that HELMs did not proactively contact health professionals or appropriate administrative staff about tapentadol and they had no materials. HELMs proactively contacted budget holders/policy makers about:

a) Versatis budgetary implications.
b) Formulary/account mapping.
c) 'Change Pain', an educational disease awareness programme tailored to each customer group to explore the problems of pain management in general and costs to society. It was also part of Grünenthal's vision of establishing the company's pain management focus in partnership with healthcare systems.
d) Contrary to the complaint, HELMs had no tapentadol materials or slide sets to use in discussions with budget holders/policy makers. HELMs did not proactively see anyone about tapentadol.

Grünenthal submitted that it routinely recorded the number of customers seen by HELMs. The company expected the HELM team to spend broadly 40% of its time working on Versatis formulary activity, and 60% between 'Change Pain' and formulary activities/account mapping. The company did not set call targets apart from a generic expectation of maintaining an industry average of 2 calls per day. There were no written instructions or briefing materials related to call rates.

Grünenthal submitted that subject to the comment directly below, no Grünenthal staff called upon health professionals or appropriate administrative staff about tapentadol proactively and there were no proactive materials available for tapentadol.

Medical information triaged all enquiries. This resulted in a response to the enquirer using a verbal response and/or a standard (approved) letter where applicable. All was logged in MedInfo Sys. Where a request was made for a member of the medical department to present information on tapentadol, an MSL might call. MSLs were all PhD scientists with a background in neuroscience or a related area. There was a MOR-NRI approved slide set and a tapentadol approved slide set which were only shown on specific request. These slide sets and certification forms were provided.

As from 29 January 2010, Grünenthal had run discrete advisory boards which were an essential preparatory part of understanding a disease area, were not promotional and were an accepted way of gauging external environment and future opportunities. Also, the agenda and interactive nature of the meetings were made clear (eg 18 March 2010 meeting), the number of attendees was limited and honoraria paid was not disproportionate given the standing of the invited attendees and input expected from them. These meetings sought advice on the development of tapentadol, line extension, commercial positioning and messaging, and health technology appraisals. All had been certified. All were subject to confidentiality agreements and service contacts and a customary fee was paid to members of the advisory board. Details were given below, and copies of the agendas and certificates were provided.

a) 18 March –Task Force advisory board (17 national clinical leaders in pain management – data review and advice on the communication of tapentadol's unique mode of action), London.
b) 30 May – Round Table – a special interest group on neuropathic pain (NeuPSIG) (5 clinical pain specialists – advice on neuropathic pain management) Athens.
c) 24 June 2010 –Task Force advisory board (16 attendees – advice on positioning of tapentadol in a pain management algorithm), London.

d) 30 June 2010 – Mock drug and therapeutic committee application advisory board (9 clinicians and budgetary influencers – advice on how to construct an application) Stokenchurch, Head office.
e) Media Task Force – media clinicians advisory board on communicating pain information in the media – to come.

Grünenthal noted that the complainant referred to contacting 3,000 health professionals. Grünenthal submitted that the issue was dealt with to the satisfaction of the MHRA and appropriate procedures had now been put in place.

Grünenthal submitted that since 29 January 2010, no health professionals or appropriate administrative staff had been contacted in a similar manner as was the substance of the MHRA complaint (ie a proactive advance notification letter).

Grünenthal submitted that it had at all times maintained high standards, had not brought discredit to or reduced confidence in the industry and in particular had not promoted an unlicensed medicine. High standards had been maintained and, therefore, Grünenthal was not in breach of Clause 9.1. Promotion had not occurred before the marketing authorization of tapentadol and Clause 3.1 had not been breached following the MHRA initial review. Finally, following MHRA guidance, Grünenthal had complied in every way with Clause 2.

As stated above, with a view to ensuring its continuing compliance, Grünenthal had submitted to the pre-vetting of promotional materials for tapentadol.

Finally, Grünenthal submitted that it was very concerned that this was an anonymous complaint unaccompanied by evidence. Grünenthal trusted the Panel would view this complaint in context; the burden of proof should lie with the complainant and its evidence, of which there was none. Nevertheless, until this complaint was resolved, only medical information would respond to enquiries, even if an MSL or HELM visit had been requested or was pending.

In response to a request for further information, Grünenthal explained that the HELMs were informed of the action taken by the MHRA and the subsequent changes they would have to make to what they did and said with regard to tapentadol in face-to-face meetings. These meetings were held to update staff on the progress and issues with regard to the ongoing dialogue with the MHRA through January to April 2010. It was explained that the MHRA had queried the company's procedures with regard to advanced notification for tapentadol. The briefing slides used during this period were provided; no additional written instructions were issued. Meetings were held with the HELM team on 4 February, 2 March and 28 April 2010.

At the meetings in February and March, the HELM team was clearly instructed to follow the existing Grünenthal request for information process (as outlined above) for unsolicited customer enquiries and discussion about tapentadol. Thus any spontaneous queries about tapentadol were sent to medical information for action.

Grünenthal stated that the HELMs had not engaged in any pro-active advanced notification for tapentadol following the company's agreement with the MHRA on 29 January. All requests for information for tapentadol by health professionals had been processed through the request for information process via the medical information department.

The HELM team had engaged in a formulary mapping exercise to gain an understanding of how a new medicine would be introduced in the local health economy. This process was outlined in briefing documents provided. No pro-active engagement of payers or other NHS employees had been undertaken following the company's agreement with the MHRA on 29 January. Any customer that spontaneously raised the topic of tapentadol with a HELM after 29 January would have been asked to complete a request for information form which would have been sent to the medical information department for action.

The HELMs were not given materials about tapentadol because as outlined above, no agreement was reached with the MHRA about the use of an advanced notification document.

The HELMS were instructed to use the existing request for information process for all products in June 2009 via a presentation at their monthly meeting. At the meeting on 4 February this process was reinforced. At the 28 April meeting the specific tapentadol request for information process was introduced and the HELMs instructed on its use. No written instructions were issued as effective communication was achieved verbally at the monthly meetings.

Grünenthal submitted that after it had been notified by the Authority on 28 June of this complaint all formulary mapping activities were suspended. The written briefing informing the HELMs of this was provided.

In response to a further request for more information, Grünenthal explained that the HELMs were verbally briefed at the meeting on 4 February that the company was in dialogue with the MHRA with regard to its activity for advance notification. The HELMs were instructed to ensure that they used the Grünenthal request for information process for any spontaneous questions on tapentadol and not to engage customers with proactive questions about the product during the period when the company was seeking clarification of what advance notification materials and process the MHRA would allow under its rules. As this matter was outlined in the MHRA Blue Book and the Code, the company was seeking to understand what it could undertake following discussion with the MHRA.

Grünenthal submitted that the slides used at the briefing meeting on 4 February were not modified as it believed it had a robust process in place for request for information queries through medical information for questions on tapentadol from heath professionals.

Grünenthal stated that given that the advance notification process was under review, at the HELMs briefing meeting in March it explored possible solutions bearing in mind the lack of an agreed way forward with MHRA at that point. Grünenthal did not get final resolution of this issue until its final correspondence with the MHRA on the advanced notification process in April when the MHRA indicated that it was not happy with any of Grünenthal's materials or process. Therefore, Grünenthal informed the HELMs of this and implemented the specific HELM request for information outlined above which did not involve any proactive discussion of tapentadol with health professionals.

Grünenthal explained that the formulary mapping exercise required HELMs to seek answers to a number of key business questions with regard to the decision making process in the local health care economy. The slide presentation, already provided, detailed the questions the HELMs were expected to answer to the best of their knowledge following the data mapping exercise.

The formulary mapping exercise was designed as a data collection process rather than a data giving process, ie the HELMs did not impart information but gathered it in relation to the local health economy's process; local arrangements could differ substantially. The answers to the key business questions were for internal use to appropriately prepare the organization for engaging with payer customers and healthcare systems when the marketing authorization was received.

Grünenthal had a business need to map local processes involved in getting a new product on formulary. The questions outlined were for the HELMs. They must gather information appropriately to answer these questions where possible.

This process was distinct from a proactive advance notification process undertaken by pharmaceutical organizations in response to the payer customers in the NHS needing to be prepared for the introduction of a new product and allowed under the Code.

Grünenthal explained that the HELMs visited individuals who were responsible for the approval and purchase of medicines within the NHS. They also visited those who had to gain approval for the use of medicines in the various local health economies across the country. The HELMs saw both types of customers on matters related to Grünenthal's licensed products in a proactive manner. These meetings were booked in a standard way with the HELM contacting individuals with regard to discussions on marketed pain products. Where HELMs had existing relationships with payer customers they had gathered an understanding about local formulary systems in relation to the introduction of new medicines.

The HELMs were instructed to say nothing about tapentadol and to use the request for information process for information requests through medical information department. They had not been issued with materials on tapentadol.

The mapping process required the HELM to answer a series of questions in relation to local formulary and access in preparation for the launch of a new product. These questions were a guide to aid the HELM in describing to Grünenthal how the local payer process worked and where, in this case, tapentadol might fit.

As tapentadol had been commercially available in the USA for over a year, a number of scientific papers had appeared in the medical press and such data had been presented at international scientific meeting it was not unexpected for some UK health professionals to know about tapentadol and that spontaneous questions might arise.

In summary, Grünenthal from the beginning of February 2010 had sought to comply with the recommendations on activities for advance notification with the MHRA. Being unable to resolve this process following a review based on the MHRA dialogue it stopped all advanced notification activities.

As part of Grünenthal's internal business planning process the HELMs were asked to answer a series of key business questions. This was outlined in a series of slides used to brief the team. Information on the local formulary process was collated by the HELMs from data gathering interactions with local payers. Grünenthal had suspended all formulary mapping activity following receipt of this complaint.

Grünenthal considered that it needed to ensure a clear distinction between activities related to advance notification for tapentadol, where activities were suspended at the end of January and formulary mapping activities to inform local business planning for successful market access post marketing authorization which were suspended pending resolution of this complaint.

PANEL RULING

The Panel noted that the complaint from an anonymous source to the MHRA was that Grünenthal continued to promote tapentadol prior to the grant of a marketing authorization. The MHRA had received a complaint about the matter in November 2009 and had agreed action with Grünenthal in January 2010; the case report was published in March 2010. The Panel noted that the MHRA had considered the activities in relation to the Advertising Regulations and the Blue Guide. The Panel considered that it was limited to considering Grünenthal's activities after January 2010 in relation to the Code.

The Panel noted Grünenthal's comments about the anonymous source of the complaint to the MHRA and the burden of proof. The Panel noted, as set out in the introduction to the Constitution and Procedure, that complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties.

The Panel noted that Grünenthal anticipated that tapentadol would be granted a marketing authorization in September 2010.

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 heath authorities etc.

The Panel noted that Grünenthal had begun an advance notification process for tapentadol in November 2009 ie only 10 months before it anticipated having a marketing authorization for the medicine. 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.

Information could only be supplied if the product had a significant budgetary implication. The Panel queried whether the introduction of tapentadol would have a significant budgetary implication but did not consider this was relevant to the complaint before it.

The Panel disagreed with Grünenthal's submission that the HELM position was a non-promotional role. The job description for the HELMs stated 'The aim of these positions will be to address barriers to access for specific products and increase sales of existing products by identifying prescribers, influences and decision making groups that have an influence on current provision of healthcare'. Under the heading 'Overall Purpose of the Role' reference was made to increasing patient access to Grünenthal products, maximising product usage, formulary inclusions, formulary status and ensuring patient access to Grünenthal products. HELMs were expected to have 'Selling skills with emphasis on payer NHS focus' and to 'Demonstrate ability to sell at all levels with the proven ability to overcome barriers'. They were required to have passed the ABPI Medical Representatives Examination. The heading 'Responsibilities of Job/Limits of Authority' included 'Develop and maintain knowledge of disease area, products and health economic cases for products and competition' and 'Work closely with the company's sales, health policy and head office teams to ensure access to Grünenthal products is optimal'.

The job description did not specifically refer to the HELMs' role with regard to advance notification, nor did it clearly state that it was a non-promotional role. In the Panel's view, and contrary to Grünenthal's submission, the job description described a promotional role.

The Panel noted that the HELMs had been briefed on 28 April 2010 with a presentation entitled 'Materials'. Slide 6, headed 'Portfolio Approach' stated, as the third bullet point, 'Basic tapentadol information can be given verbally'. Slide 8 'Product Specific Information' stated the following:

- 'Questions of a substantive nature relating to tapentadol must go via Medical Information.
- The response to these questions can be delivered by appropriately trained staff.
- Therefore, in compliance with the MHRA's request, materials available do not refer to tapentadol.'

It appeared, therefore, that whilst HELMs were not given any printed material regarding tapentadol, they could still talk about it. The Panel considered that this approach was wholly unacceptable. There was no guidance as to what constituted 'Basic tapentadol information' or 'Questions of a substantive nature'. Slide 9 headed 'Basic information: What can I say?' listed the permitted basic information namely the name of the products in the portfolio, when they would be available, what was or would be their indication and or cost and what was the value of the product. Slide 10 was headed 'Further questioning which may assist in helping address the KBQs [key business questions] and map the account'. They were divided into two areas 'process' and 'clinical'. The process section included questions about local protocols/guidelines and likely reaction of medicines management. The clinical section included a question about which clinical areas could the product be used in and which current therapies could the product challenge. It included the statement 'Any further requests for product specific information should be sent to Med Info via the [request for information]'. The Panel further noted that slides 13 and 14 headed 'What does tapentadol offer over existing therapies in Med Info Response' appeared to reproduce the text of a medical information letter and some bar charts which compared tapentadol with oxycodone. Although both slides were marked 'Example – not approved for distribution' there was no instructions as to whether the information could be delivered verbally by the HELMs as basic tapentadol information. The Panel was very concerned that material showing an advantage for tapentadol PR over oxycodone CR had been shown to the HELMs. At a previous meeting, 4 February, HELMs had been shown the core messages for Palexia. In the Panel's view, the more information the HELMs were given about tapentadol the more likely they were to use it to 'overcome barriers' and 'ensure patient access'.

The Panel noted Grünenthal's submission that the HELMs had not engaged in any proactive advance notification for tapentadol following an agreement with the MHRA on 29 January. It appeared that since

then the HELMs had undertaken a formulary mapping exercise to gain an understanding of how a new medicine would be introduced into the local health economy. This exercise required the HELMs to seek answers to a number of key business questions. Some of those questions were detailed in a briefing presentation, 2 March and included the following: 'Identify attitudes to [controlled drugs] and tapentadol in nociceptive neuropathic and specifically back pain'; 'Where do they see tapentadol on the analgesic ladder?'; 'Where does the customer see a new pain drug adding most value?' and 'Does [drug and therapeutics] need to be achieved before a new pain drug can be used?'. The Panel noted Grünenthal's submission that following dialogue with the MHRA in April 2010, HELMs were briefed to discuss the process issues in relation to new products in general. Further formulary mapping questions appeared in the presentation dated 28 April 2010 described above.

The Panel noted that the HELMs visited individuals responsible for the approval and purchase of medicines within the NHS; they also visited those who had to gain approval for the use of medicines in local health economies. The HELMs proactively saw both types of customers in relation to Grünenthal's licensed products (Tramacet, Versatis and Zydol) all of which were for pain relief. The Panel considered that in this regard customers would see the HELMs as medical representatives. To have that same group of people then asking questions about tapentadol or a 'new pain drug' would be seen as promotional. The Panel noted its comments above regarding the selling skills of the HELMs.

The Panel considered that the HELMs' role was not non-promotional. Their activities were not limited to a fact finding role as the nature of the questions they were to ask would raise interest and awareness in the new product and solicit questions about it. The slides presented to the HELMs about tapentadol reinforced the promotional aspect of their activity. The HELMs were expected to have selling skills and they visited the same people to tell them about licensed medicines and to ask them questions about tapentadol and/or 'a new pain drug'. In the Panel's view asking such questions amounted to the promotion of tapentadol before the grant of its marketing authorization. Thus a breach of Clause 3.1 was ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that Clause 2 of the Code was a sign of particular censure and reserved for such. The supplementary information to that clause listed examples of activities likely to be in breach of Clause 2 and included promotion prior to the grant of a marketing authorization. The Panel considered that to brief a team, employed for its selling skills, to raise the profile of tapentadol and/or 'a new pain drug' just weeks before the expected grant of a marketing authorization was unacceptable. The Panel was very concerned about the failure to provide the HELMs with clear written instruction and this was a particularly serious omission given the concerns raised by the MHRA about the activity. The Panel considered that the activity amounted to a softening of the market. Such activity brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was extremely concerned about Grünenthal's activities with regard to the advanced notification of tapentadol. The MHRA had provided advice to the company following a mailing about tapentadol to 3,000 people. Since being in correspondence with the MHRA, Grünenthal had used a team of HELMs to gather information about, inter alia, attitudes to tapentadol and how to get 'a new pain drug' on to a formulary. The HELMs were expected to have selling skills and saw some of the same people about licensed and unlicensed medicines. The HELMs were expected to work closely with the sales team. Briefings to HELMs about this matter after the intervention of the MHRA were inadequate. Overall the Panel considered that Grünenthal's activity amounted to the promotion of tapentadol prior to the grant of its licence. In the Panel's view the HELMs' activities did not constitute the advance notification of tapentadol as no information was being supplied that showed that the product would have a significant budgetary effect. The Panel considered that overall Grünenthal's actions were unacceptable. 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. The Panel noted Grünenthal's submission that on receipt of this complaint it had suspended all formulary mapping activities.

COMMENTS FROM GRÜNENTHAL ON THE REPORT

At the consideration of the report the representatives from Grünenthal apologised and accepted that there had been failings that had led to the Panel's rulings. It was difficult for the company to prove what was done (and what was not done) in the absence of evidence. The HELM briefing slides had not been properly checked/approved and had failed to state what could not be done. The representatives stated that in order to avoid similar breaches of the Code in the future it had: put in place new policies, procedures and structures; updated the HELMs' job description; retrained final signatories; introduced an electronic approval system; proposed the appointment of a Code compliance manager; updated all Code related standard operating procedures; arranged an audit by external consultants; reviewed all HELM material and disciplining action for relevant staff was under way.

APPEAL BOARD CONSIDERATION

The Appeal Board noted from the company representatives that Grünenthal had originally set up a market access team comprised of two managers and five HELMs to try to limit the extensive off-label use of Versatis and to gain market access for its portfolio of licensed pain medicines. Part of the HELMs' role was to promote Grünenthal's medicines. The company had then used this same team, with the same job description, to work on the advance

notification of tapentadol. In response to a question the representatives described the reasons why the company considered that the introduction of tapentadol would have a significant budgetary impact. The Appeal Board was very concerned about the conduct of Grünenthal. The prohibition on the promotion of a medicine prior to the receipt of its marketing authorization should have been well understood by the two senior managers representing the company who themselves had referred to their many years of experience in the industry. In that regard the deployment of the HELMs to work on the advance notification of tapentadol should have been tightly controlled from the outset. Even in the absence of this, it appeared that Grünenthal had not taken the opportunity to thoroughly review the HELMs' role and responsibilities when the MHRA had determined that, in providing advance notification, they had infact promoted tapentadol prior to the grant of its marketing authorization. Although changes had been made to the way the HELMs worked at this point, in that they had no role in relation to advance notification, the account mapping and other activities which they carried out were considered by the Panel to still amount to the promotion of a medicine prior to the grant of its marketing authorization. This was unacceptable.

The Appeal Board was very concerned to learn that the market access team had generated presentations and briefing materials for the HELMs which had not been certified. In that regard the Appeal Board queried whether the senior management team had exercised sufficient control over the market access team especially considering it was newly appointed, had responsibilities for an unlicensed medicine and the MHRA's involvement in the matter.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of Grünenthal's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted as soon as possible. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

FURTHER APPEAL BOARD CONSIDERATION

Upon receipt of the audit report (October 2010) the Appeal Board noted that Grünenthal had agreed compliance plans which would address all the areas recommended for attention and this was already being implemented.

The Appeal Board decided that a second audit should be carried out in February 2011 when it would expect the recommendations in the audit report to be implemented. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the second audit report (delayed until March 2011) the Appeal Board was encouraged by Grünenthal's progress since October but considered that the company still needed to demonstrate that it understood the importance of compliance. The Code and its requirements needed to become embedded into all levels of the company.

The Appeal Board decided that a third audit should be carried out in September when it would expect the recommendations in the audit report to be implemented. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon consideration of the third audit the Appeal Board was concerned that it still appeared that the company had not really understood the seriousness of the situation. The Appeal Board was extremely concerned to note errors in the response from Grünenthal to the recommendations from the March 2011 audit (part of the preparation for the September 2011 audit). This was unacceptable. It was hard to believe, given the recommendation in March that the company should be confident that all the Versatis material was clear regarding the licensed indication, that the company had not been precise about what had been done. Senior employees had not taken decisive action to implement the recommendation. The failure of senior employees to respond in full to questions at the audit about that recommendation led the Appeal Board to question the company's stated commitment to compliance.

The Appeal Board decided that, in accordance with Paragraph 11.3 of the Constitution and Procedure, Grünenthal should be publicly reprimanded in relation to the misinformation in its response to the Authority. Prior to the third audit the Appeal Board was extremely concerned about the apparent lack of demonstrated change in the company culture. It noted that some activities had been started and these might improve the situation. A new general manager was appointed in October. The Appeal Board decided that a fourth audit of Grünenthal should take place by mid February 2012. Upon receipt of the report for that audit, it would decide whether further action was needed.

Upon consideration of the fourth audit report the Appeal Board noted that Grünenthal had undergone changes in senior staff including a new general manager. There appeared to be a different culture in the company and a more positive attitude to compliance. The Appeal Board considered that there had been encouraging progress since the last audit. On the basis that the company adopted an approach of continual improvement the Appeal Board considered that no further action was required.

Complaint received	**25 June 2010**
Undertaking received	**7 September 2010**
Appeal Board consideration **22 September 2010, 10 November 2010,** **28 April 2011,16 November 2011, 22 March 2012**	
Interim case report published	**4 November 2010**
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