GENERAL PRACTITIONER v GRÜNENTHAL

Promotion of Palexia

A general practitioner complained that a four page dosing and titration leavepiece for Palexia SR (tapentadol prolonged release) issued by Grünenthal was misleading with regard to the licensed patient population.

Page 2 was headed 'Palexia SR – Unlock the potential in patients not currently taking strong opioids'. Under a sub-heading of 'Start low, go slow', advice on dosage in patients who were currently not taking strong opioids was given.

The complainant noted that Palexia SR was indicated for the management of adults with severe chronic pain which could be adequately managed only with opioid analgesics.

The complainant submitted that the leavepiece was misleading particularly on the second page where, in his view, it attempted to ask prescribers to prescribe Palexia SR for patients not currently taking strong opioids. This appeared to be outside of the licensed guidance and therefore in breach of the Code in promoting such an indication. The complainant queried why someone would want to take Palexia SR if their pain was adequately controlled by a strong opiate because there appeared to be no discernable advantages.

The detailed response from Grünenthal is given below.

The Panel noted that the leavepiece entitled 'Starting to unlock the potential of Palexia SR (tapentadol prolonged release tablets): Dosing and titration guidance' featured on the bottom left hand corner of the front page a statement about its licensed indication: 'Palexia SR is indicated for the treatment of chronic pain in adults, which can be adequately managed only with opioid analgesics'. Page 2 began with the claim at issue and the prominent heading 'Palexia SR-Unlock the potential in patients not currently taking strong opioids'. Dosage recommendations in patients currently not taking opioid analgesics appeared beneath the subheading 'Start low, go slow'.

According to its summary of product characteristics (SPC), Palexia SR was indicated for the management of severe chronic pain in adults, which could be adequately managed only with opioid analgesics.

The Panel considered that the claim at issue implied that Palexia SR was indicated for use in all patients not currently taking strong opioids and that was not so. Its use was restricted to those patients who could be adequately managed only with opioid analgesics. Neither the claim, nor its immediate visual field nor the text below described the patient population for whom Palexia was indicated. The claim was inconsistent with the SPC and misleading in this regard. The Panel noted that a statement about the licensed indication appeared on the front page of the leavepiece but considered that this did not counter the misleading nature of the claim at issue and thus breaches of the Code were ruled. The Panel considered that this ruling covered the allegation and did not consider that the circumstances warranted an additional ruling in relation the need to maintain high standards. No breach of the Code was ruled.

Upon appeal from Grünenthal the Appeal Board noted from Grünenthal that the licensed indication 'for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics' meant that when a health professional considered that an opioid analgesic was appropriate, that health professional could consider prescribing Palexia SR to opioid naïve patients. 65% of patients in the Palexia SR registration trials had had no prior opioid experience and less than 5% had previously taken a strong opioid.

The Appeal Board noted that the indication for Palexia SR appeared on the bottom left hand corner of the front page of the leavepiece. The company submitted that the indication was stated there so as to be near the black triangle which had to be adjacent to the most prominent display of the product name which was in the bottom right corner of the front page.

The Appeal Board noted the claim at issue and heading to page 2 stated 'Palexia SR – Unlock the potential in patients not currently taking strong opioids'. The Appeal Board noted from the company that 'strong' was included because initiation of Palexia SR was the same for patients who had not taken opioid analgesics and those that were already taking a weak opioid analgesic. Therefore page 2 dealt with these two groups of patients. Whereas page 3 headed 'Palexia SR – Unlock the potential in patients currently taking strong opioids' dealt with switching patients who were currently taking a strong opioid analgesic to Palexia SR.

The Appeal Board noted that much of the wording in the leavepiece was derived from the SPC. The Appeal Board considered that including the indication on the front page of the leavepiece sufficiently described those patients for whom

Palexia SR was indicated. The Appeal Board considered that the claim at issue on page 2 of the leavepiece was not inconsistent with the particulars listed in the SPC nor was it misleading in this regard. The Appeal Board ruled no breaches of the Code. The appeal was thus successful.

A general practitioner complained about a four page dosing and titration leavepiece (ref P11 0066) for Palexia SR (tapentadol prolonged release) issued by Grünenthal Ltd.

Page 2 of the leavepiece was headed 'Palexia SR – Unlock the potential in patients not currently taking strong opioids'. Under a sub-heading of 'Start low, go slow', advice on dosage in patients who were currently not taking strong opioids was given. Page 3 of the leavepiece was headed 'Palexia SR – Unlock the potential in patients currently taking strong opioids' and featured information on how to switch patients already on opioids to Palexia SR.

COMPLAINT

The complainant noted that Palexia SR was indicated for the management of adults with severe chronic pain which could be adequately managed only with opioid analgesics.

The complainant submitted that the leavepiece was misleading particularly on the second page where, in his view, it attempted to ask prescribers to prescribe Palexia SR for patients not currently taking strong opioids. This appeared to be outside of the licensed guidance and therefore in breach of the Code in promoting such an indication. The complainant queried why someone would want to take Palexia SR if their pain was adequately controlled by a strong opiate because there appeared to be no discernable advantages.

The third page attempted to suggest a way to switch patients on strong opiates onto Palexia SR which was within the licensed indications.

In summary, the complainant submitted that the leavepiece was possibly in breach of Clauses 7 or 9 of the Code.

When writing to Grünenthal, the Authority asked it to respond in relation to Clauses 3.2, 7.2 and 9.1 of the Code.

RESPONSE

Grünenthal submitted that the marketing authorization for Palexia SR was, as stated in the summary of product characteristics (SPC), 'Palexia SR is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics'. As such, adult patients who were not on a strong opioid could be prescribed Palexia SR if they had severe chronic pain which could be adequately managed only with opioid analgesics.

Given that the promotion of Palexia SR was in line with the terms of its marketing authorization and consistent with the particulars listed in its SPC, Grünenthal submitted that it was strictly adhering to Clause 3.2. Furthermore, the data presented was an accurate and unambiguous reflection of the marketing authorization and SPC, thus the company denied a breach of Clause 7.2. By complying with Clauses 3.2 and 7.2, Grünenthal believed that it had maintained high standards at all times as defined in Clause 9.1.

PANEL RULING

The Panel noted that the leavepiece entitled 'Starting to unlock the potential of Palexia SR (tapentadol prolonged release tablets): Dosing and titration guidance' featured on the bottom left hand corner of the front page a statement about its licensed indication: 'Palexia SR is indicated for the treatment of chronic pain in adults, which can be adequately managed only with opioid analgesics'. Page 2 began with the claim at issue and the prominent heading 'Palexia SR-Unlock the potential in patients not currently taking strong opioids'. Dosage recommendations in patients currently not taking opioid analgesics appeared beneath the subheading 'Start low, go slow'.

According to its SPC, Palexia SR was indicated for the management of severe chronic pain in adults, which could be adequately managed only with opioid analgesics.

The Panel considered that the claim at issue on page 2 implied that Palexia SR was indicated for use in all patients not currently taking strong opioids and that was not so. Its use was restricted to those patients who could be adequately managed only with opioid analgesics. Neither the claim, nor its immediate visual field nor the text below described the patient population for whom Palexia was indicated. The claim was inconsistent with the particulars listed in the SPC and misleading in this regard. The Panel noted that a statement about the licensed indication appeared at the bottom of the front page of the leavepiece but considered that this did not counter the misleading nature of the claim at issue and thus a breach of Clauses 3.2 and 7.2 was ruled. The Panel considered that this ruling adequately covered the allegation and did not consider that the circumstances warranted an additional ruling in relation to Clause 9.1 and the need to maintain high standards. No breach of Clause 9.1 was ruled.

APPEAL BY GRÜNENTHAL

Grünenthal submitted that Sections 4.1 and 4.2 of the Palexia SR SPC set out the licensed indication and the dosing information for clinical use respectively (see below). The text from these sections of the SPC was replicated and used in the leavepiece at issue in the interests of patient safety. The licensed indication did not state that a strong opioid was required to adequately manage severe

chronic pain. Furthermore, in the registration trials used to obtain the marketing authorization for Palexia SR 65.5% of patients had no prior opioid experience (Lange *et al* 2010) and less than 5% of patients had experience on strong opioids (data on file).

> '4.1 Therapeutic indications
> Palexia SR is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.
>
> 4.2 Posology and method of administration
> The dosing regimen should be individualised according to the severity of pain being treated, the previous treatment experience and the ability to monitor the patient.
>
> Palexia SR should be taken twice daily, approximately every 12 hours.
>
> Initiation of therapy
>
> **Initiation of therapy in patients currently not taking opioid analgesics** [emphasis added]
>
> Patients should start treatment with single doses of 50mg tapentadol as prolonged-release tablet administered twice daily.
>
> **Initiation of therapy in patients currently taking opioid analgesics** [emphasis added]
>
> When switching from opioids to Palexia SR and choosing the initial dose, the nature of the previous medicinal product, administration and the mean daily dose should be taken into account. This may require higher initial doses of Palexia SR for patients currently taking opioids compared to those not having taken opioids before initiating therapy with Palexia SR.
>
> Titration and maintenance
>
> After initiation of therapy the dose should be titrated individually to a level that provides adequate analgesia and minimises undesirable effects under the close supervision of the prescribing physician.
>
> Experience from clinical trials has shown that a titration regimen in increments of 50mg tapentadol as prolonged-release tablet twice daily every 3 days was appropriate to achieve adequate pain control in most of the patients.
>
> Total daily doses of Palexia SR greater than 500mg tapentadol have not yet been studied and are therefore not recommended.'

Grünenthal submitted that the leavepiece was developed to ensure that once the physician had made an appropriate clinical decision to treat patients with Palexia SR, administration guidance of the treatment was available according to the marketing authorization and information detailed in the SPC. Providing dosing and titration guidance to the prescriber supported the use of Palexia SR to help ensure adequate clinical efficacy and patient safety. To ensure that the dosing and titration guidance was clinically meaningful, dose ratio information was required. This was not included in the SPC and the provision of this information was a key aim of the leavepiece.

The front cover of the leavepiece clearly stated:

- product name
- purpose
- that Palexia SR was indicated for the treatment of severe chronic pain in adults, which could be adequately managed only with opioid analgesics
- that tapentadol was a Controlled Drug, Schedule 2
- that health professionals could find the prescribing information on the back page.

The health professional would see the front cover first which defined the context of the leavepiece in terms of a licensed treatment population. If the leavepiece was read from the back cover first, then the prescribing information was prominently displayed, reiterating the licensed indication. In conclusion, the health professional would see on either the front or back pages the licensed indication for Palexia SR.

Grünenthal submitted that once the health professional turned to the inside of the leavepiece there was a single double page spread. This provided information from the SPC, indeed the text was replicated from the posology and method of administration section of the SPC (Section 4.2), and how to initiate Palexia SR once a suitable patient had been identified. This patient could either be currently taking an opioid analgesic (page three) or not (page two). Therefore the context of the title of page two 'Palexia SR – Unlock the potential in patients not currently taking strong opioids' had already been made clear through the licensed indication stated on page one. Grünenthal noted that all advice and each statement on page two was referenced to the SPC.

Grünenthal submitted therefore that it was clear to the health professional that Palexia SR was to be prescribed for adults who required treatment for severe, chronic pain, which could be adequately managed only with opioid analgesics. Therefore the leavepiece did not breach Clause 3.2. Moreover, the leavepiece logically laid out the nature of the product prior to providing dosing advice; therefore it did not breach Clause 7.2.

In summary, Grünenthal submitted that the claim was consistent with the SPC and therefore not misleading. The material was sufficiently complete to enable the health professional to form his/her own opinion. Grünenthal thus denied breaches of Clauses 3.2 and 7.2.

Grünenthal noted that the leavepiece had been withdrawn and it provided its revised version where the claim at the top of the front page had been changed. Grünenthal also provided a copy of its appeal slides.

COMMENTS FROM THE COMPLAINANT

The complainant maintained that page 2 of the leavepiece in question was misleading. In the complainant's view it would have made more sense to have had information on how to treat patients already taking a strong opioid on page 2 and not page 3 but due to the limited likely market share this medicine would achieve the complainant suspected the bigger market long term was in the creep into opiate naïve patients. Page 2 of the leavepiece made a stab at a market outside the existing licence.

APPEAL BOARD RULING

The Appeal Board noted Grünenthal's submission that the licensed indication 'for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics' meant that when a health professional considered that an opioid analgesic was appropriate, that health professional could consider prescribing Palexia SR to opioid naïve patients. In that regard, in the registration trials used to obtain the marketing authorization for Palexia SR, 65.5% of patients had no prior opioid experience (Lange *et al*) and less than 5% of patients had previously taken a strong opioid (data on file).

The Appeal Board noted that Palexia SR had mu-agonistic opioid and additional noradrenaline reuptake inhibition properties. The SPC stated that all patients treated with active substances that had mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction. It also stated that the pharmacotherapeutic group for Palexia was 'Analgesics; opioids; other opioids'.

The Appeal Board noted that the indication for Palexia SR appeared on the bottom left hand corner of the front page of the leavepiece. The company submitted that the indication was stated there so as to be near the black triangle which had to be adjacent to the most prominent display of the product name which was in the bottom right corner of the front page.

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The Appeal Board noted that much of the wording in the leavepiece was derived from the SPC. The Appeal Board considered that including the indication on the front page of the leavepiece sufficiently described those patients for whom Palexia SR was indicated. The Appeal Board considered that the claim at issue on page 2 of the leavepiece was not inconsistent with the particulars listed in the SPC nor was it misleading in this regard. The Appeal Board ruled no breaches of Clauses 3.2 and 7.2. The appeal was thus successful.

During its consideration of this case the Appeal Board expressed concern that although the front page of the leavepiece stated that 'Tapentadol is a Controlled Drug, Schedule 2' it was not sufficiently clear in the leavepiece that Palexia SR was an opioid analgesic and the clinical implications this might have. The Appeal Board requested that Grünenthal be so advised.

Complaint received **30 September 2011**

Case completed **7 December 2011**