

Code of Conduct complaints relating to activities directed at the general public December 2008

The Medicines Australia Code of Conduct (Section 16.3) provides for the publication on the website of information regarding complaints that involve activities directed towards members of the general public. Section 16.3 states that this information will include the following:

- a) The name of the company against which a complaint has been lodged
- b) The name of the complainant, where appropriate
- c) The product, behaviour, conduct and/or promotional material subject to complaint
- d) A summary of the complaint, response and deliberations of the Code of Conduct Committee
- e) The section of the Code, if any, which was breached and the reasons for finding the breach
- f) Any sanctions imposed for the breach

The information shall be released following the exhaustion of all appeals procedures and the outcome of any appeal is known.

- 964 Cymbalta Media Release
- 982 Exelon Media Release

These two complaints have been reviewed by the Code of Conduct Committee.

Cymbalta 964

Subject Company: Eli Lilly Australia (ELA) and Boehringer Ingelheim

Complainant: Lundbeck

Product: Cymbalta

Complaint:

Lundbeck alleged that a media release issued by ELA on 29 May 2008 to announce the PBS listing of Cymbalta was promoting a prescription medicine to the general public. Lundbeck further alleged that claims for duloxetine (Cymbalta) were misleading, inaccurate and suggested the product could be used for an unapproved indication.

Sections of the Code:

The media release was alleged to be in breach of the following Section of the Code:

- 1.3 False or Misleading Claims
- 1.3.1 Unapproved products and indications
- 9.2.1 Relationship with the General Public (Product Specific Media Statements)
- 9.2.3 Relationship with the General Public (Product Specific Media Statements)
- 9.4 Promotion to the General Public

Response:

ELA denied that the media release promoted the medicine to the general public. ELA further argued that the media release was consistent with the approved Product Information and was therefore not in breach of Section 1.3 of the Code.

Code of Conduct and Appeals Committee determinations

- In a majority decision the Committee found a breach of Sections 1.3, 1.3.1 and 9.4 of the Code.
- In a unanimous decision a breach of Section 9.2.1 of the Code.
- In a unanimous decision no breach of Section 9.2.3 of the Code was found.
(Decisions confirmed by the Appeals Committee.)

Sanction

- Withdraw the media release from further use, including removal from all websites over which ELA has control.
- Pay a fine of \$100,000.

Consideration of the complaint

The Committee noted that the Cymbalta was jointly marketed by ELA and Boehringer Ingelheim but ELA had responded to the complaint on behalf of both companies.

Members also noted the statement from ELA that it had sought advice from Medicines Australia prior to issuing the media release and had made changes as suggested by Medicines Australia. ELA acknowledged that requesting advice from the Secretariat does not avoid any subsequent complaint being upheld, but the consultation had led to an expectation that Medicines Australia would have identified all areas of concern and that the revised media release was Code compliant. The Committee commented that while Medicines Australia staff may provide comment on material sent to them, this advice is not binding on the Committee which could make a finding in relation to potential breaches of the Code.

The Committee noted that the approved indication for Cymbalta was for the treatment of major depressive disorder. It was also noted that:

- the Cymbalta Product Information (PI) refers to some analgesic activity in rodent models for persistent, inflammatory or neuropathic pain but not acute or arthritic pain; and
- the PI also states that musculoskeletal pain was a common side effect reported with the use of Cymbalta during clinical trials.

The majority view was that the references in the PI did not provide a basis to make a claim that may be interpreted to mean the product treated pain.

From its review of referenced studies published in peer reviewed journals the Committee commented that there did not appear to be a sufficient body of evidence that Cymbalta offered analgesic effects superior to placebo or to other currently available antidepressants. It was noted that the studies referenced by ELA in its response to the complaint were all placebo controlled studies; there were no studies comparing duloxetine with other antidepressants in their effects on pain associated with depression. While noting that some of these studies were funded by ELA, the Committee accepted that this did not mean that the studies were not conducted appropriately, further noting that the studies had been published in peer-reviewed journals. There appeared to be evidence of some efficacy of duloxetine for pain associated with fibromyalgia syndrome but not musculoskeletal (back and joint) pain as was suggested in the media release.

The survey undertaken by ELA, quoted in the media release, was considered to be an attempt to position Cymbalta as being effective in treating back and joint pain by claiming that 78% of Australians were unaware that that depression can be associated with physical symptoms such as these. Members were concerned that the survey appeared to have been conducted with the intention of creating the perception that there was an unmet need, and then to promote Cymbalta as the solution to this need.

There was strong consensus amongst the Committee that ELA had attempted to draw attention to the treatment of physical pain symptoms associated with depression with Cymbalta to the general public. This was considered to be outside the approved indication for Cymbalta, which is solely for the treatment of major depressive disorder, and had no place in a Press Release for public consumption. It was considered that there was no sufficiently supportive statement in the Cymbalta PI of efficacy in painful conditions in association with depression.

The Committee was of the view that the media release was promotional to the general public and that it created the impression that there was an unmet need that could be met with a new, PBS-listed treatment for depression and pain. It was considered that a key focus of the media release was on the relief of pain rather than on the approved indication of major depression. For these reasons it was outside the scope of permitted press releases.

Whilst the Committee noted that there was no evidence that information from the media release had been used by healthcare professionals or published in any media, the Committee was satisfied that it had been the intention for the information to be widely published, whether or not anyone took it up.

Some members of the Committee were concerned that statements by reputable health consumer organisations such as SANE would have resonance with members of the general public and had been used in the media release to support ELA's messages. Members agreed that Medicines Australia should write to SANE informing it of the complaint once it was finalised.

In a unanimous decision the Committee found a breach of Sections 9.2.1 and 9.4 of the Code on the basis that the media release was promoting a prescription medicine to the general public. In a majority decision the Committee found a breach of Sections 1.3 and 1.3.1 of the Code on the basis that there was insufficient evidence to support the use of Cymbalta as a treatment for physical pain associated with depression. Whilst there may be material sufficient to enliven a debate in a medical setting, it was insufficient, particularly in the light of the Product Information to support the statements and connection made in a public context. Hence, this was also found to be a promotion outside the approved indication for Cymbalta. The Committee did not find a breach of Section 9.2.3 as based on the submission before it, it was the Committee's understanding that there was no material distributed with the media release. The survey whilst it was referred to in the release was not based on the Committee's understanding provided with the Cymbalta media release.

Sanctions

Having found several breaches of the Code the Committee considered what sanction/s should be imposed. The Committee unanimously determined that ELA should:

- Withdraw the media release from further use, including removal from all websites over which ELA has control.
- Pay a fine of \$100,000.

Appeal

ELA lodged an appeal stating that the press release should be considered as a whole when considering the representations which were said to be misleading and promotional. At no stage did ELA position Cymbalta to be a treatment for pain in general. The press release announced the availability of a new treatment option for major depressive disorder (MDD). The press release informed the reader that Cymbalta is a new product which treats both MDD and the lesser known associated physical symptoms. Painful physical symptoms are only mentioned in the context of MDD.

ELA also stated that the Code of Conduct Committee had failed to consider that the Cymbalta PI contains references in the Clinical Trials section and the medical literature about the analgesic effect on humans who suffer from MDD.

ELA asked that the Appeals Committee overturn the Code Committee's findings of a breach of Sections 1.3, 1.3.1, 9.2.1 and 9.4 of the Code. In addition, ELA argued that if the Press Release is still found in breach of the Code, that the fine should be considerably reduced.

Response to Appeal

Lundbeck did not agree that the Code Committee had made an error of any kind. Lundbeck asserted that ELA had not presented any evidence or argument in the appeal that had not already been taken into consideration by the Code Committee. Lundbeck asserted that there is insufficient evidence to support a claim that Cymbalta is efficacious in treating the physical symptoms of depression, and therefore requests that the Appeals Committee uphold all the findings of the Code Committee. Lundbeck further argued that the sanctions should remain unchanged.

Consideration of the appeal

Members noted that the media release was issued on behalf of Eli Lilly and Boehringer Ingelheim (BI), however ELA had taken the lead in responding to the complaint and lodging an appeal. This was supported by BI.

The Appeals Committee considered the advice provided by the Code Secretariat to Eli Lilly on a draft media release prior to it being issued. Members acknowledged that such advice is always provided in the understanding that the Code Committee or Appeals Committee is not bound by the Secretariat's advice. It is well understood that members of the Secretariat do not approve any activity or material and it remains the responsibility of a company for its activities or materials.

The following outlines the appeal presentation made by ELA.

The media release contained a number of simple facts that did not go further than a qualitative and quantitative description of the product and its mechanism of action and information on the safety profile of the medicine.

ELA/BI did not ignore the advice of Medicines Australia (MA) in relation to the media release.

- the paragraphs identified by MA to be of concern were amended or deleted. ELA made three significant changes to the media release.
- Other paragraphs identified as potentially of concern were carefully considered and ELA was of the view that the Product Information (PI) and other evidence supported statements in the media release.

Cymbalta was not referred to as a treatment for pain

- The only reference to physical symptoms was in association with MDD.
- The press release mentions depression thirteen times and pain only twice, or six times if you count both 'pain' and 'physical symptoms'.
- The media release was not about Cymbalta in pain relief.

The press release did not make comparative statements

- Referring to a "new" listing on the PBS is not a comparative statement.

Physical symptoms are associated with MDD

- Diagnostic tools such as DSM-IV acknowledge that depression is associated with physical symptoms and rating scales such as the HAM-D scale required by the TGA and FDA includes somatic symptoms such as aches and pains in the core rating scale for antidepressants.
- Lundbeck both acknowledge physical symptoms such as headache and backache and highlight the importance of their treatment in educational, clinical and promotional materials.
- An Australian expert review concluded "*Pain and depression are linked by overlapping phenomenology, neurobiology and therapy. They are mutually interacting and the interaction has significant treatment and outcome implications*".
- There are 9 independent placebo controlled studies which identified physical symptoms in association with MDD and demonstrated efficacy in relation to pain associated with depression.

The Cymbalta PI does refer to human data regarding physical symptoms of depression

- The body of evidence supports that Cymbalta does treat painful physical symptoms of depression, and the TGA has accepted this evidence in the PI.
- The Code Committee failed to consider that the PI contains information in the clinical trials section about efficacy in treating physical symptoms of depression. The Cymbalta PI states "*In addition to the HAM-D17 total score, several other measures were included in the evaluation of efficacy of duloxetine. HAM-D17 Depressed Mood Item (Item 1), the Anxiety Sub-factor of the HAM-D17, the Patient Global Impressions (PGI) Improvement Score, bodily pain as measured by Visual Analog Scale (VAS), and the Quality of Life in Depression rating scales were also examined. In the four studies where duloxetine demonstrated statistical superiority over placebo as measured by improvement in the HAM-D17 total score, results were also positive for the additional measures at doses of 60mg to 120mg per day*".
- The TGA has reviewed and approved these data to be included in the Cymbalta PI.

The Cymbalta media release was educational

- Press releases are permitted under the Code to inform the public of the availability of a new medicine.
- The press release did:
 - Announce a new product for treatment of MDD;
 - Explain the method of action;
 - Educate/inform reader about lesser known physical symptoms of MDD;
 - Educate/inform the reader that there is still a stigma associated with MDD;
 - Educate/inform the reader that the new product available for treatment of MDD treats both the emotional and lesser known physical symptoms of MDD.
- The press release did not refer to pain in isolation of MDD;
 - It did not make comparative claims; and
 - It was not designed to create an 'unmet need'.

Sanction Imposed

- The fine imposed by the Code Committee is excessive given the circumstances
- The Committee's ruling and Lundbeck's submissions infer a repeat breach of the Code. However, none of the criticisms of the Cialis press release (complaints 947 and 948) apply to the Cymbalta press release.
- After the Cialis ruling, ELA changed internal procedures to ensure a similar situation did not recur:
 - press release was submitted to MA for comment and suggestions were taken on board;
 - made specific mention to dosage, precautions, side effects and contraindications; and
 - only used balanced statements about the product.
- ELA/BI submit there was no repeat breach.

Conclusion

- Depression is a multi-symptom illness of which physical symptoms are an integral part.
- Cymbalta does treat physical symptoms of MDD.
- Cymbalta PI clearly refers to efficacy in the treatment of physical symptoms of depression.
- The press release informed the reader about a new product and educated the reader about the lesser known physical symptoms of MDD.
- The media release did not make comparative claims.
- The media release adhered to relevant Code Guidelines.
- The fine imposed was excessive.

The Chairman of the Appeals Committee clarified two matters raised by ELA in their presentation.

- The Appeals Committee is constituted differently to the Code of Conduct Committee and no-one on this Committee was present at the Code of Conduct Committee meeting.
- The extract of the Code Committee minutes do not make any reference to the Cialis media release in relation to the Cymbalta media release complaint. This reference has only been raised by Lundbeck.

The following outlines the presentation in response to the appeal made by Lundbeck.

- The Lundbeck Institute (whose materials ELA had referred to in its appeal presentation) is independent from Lundbeck Australia. The Institute supports education for psychiatrists.
- ELA ignored the advice of MA regarding the need for adequate evidence and an approved indication. Any procedural changes made by ELA were inadequate.
- ELA (and Boehringer Ingelheim) have not presented anything new in their appeal to indicate that the Code Committee had erred in its findings.
- This matter is still unresolved after nearly 6 months.

Breach Sections 1.3 and 1.3.1

- MA recognised that ELA/BI was promoting the off-label use of Cymbalta as indicated by its comments in the Secretary's email to ELA.

- the diagnosis of depression criteria in DSM IV does not include any physical symptoms such as pain as being symptoms relevant to a diagnosis of depression. TGA indication of Cymbalta, which is the treatment of MDD, was based on the DSM IV criteria. The promotion of Cymbalta for the physical symptoms of depression in the media release is therefore off-label.
- There are three statements in the Cymbalta PI pertaining to pain:
 - analgesic activity in rodents;
 - myalgia, neck pain, abdominal pain are listed as common side effects; and
 - bodily pain as measured by the Visual Analog Scale (VAS) - at doses of 60 - 120mg/day - this was secondary efficacy measure.
- The approved daily dose of Cymbalta in Australia is 60mg/day. The studies cited by ELA ranged from 40mg to 120mg daily. Only studies at 60mg per day are relevant, which is the approved dose.
- Data on the VAS that is mentioned in the PI, and which used 60mg/day, are two studies that:
 - Were not designed for the purpose of addressing the efficacy of duloxetine on pain in patients with depression.
 - Had no pain-specific entry criteria for patients in either study.
 - Where VAS was a secondary outcome measure in both studies.
 - Were not studies designed to demonstrate statistically significant results in these secondary outcome measures.
 - Patients were permitted to take analgesics during the course of both of these studies.
 - One study demonstrated that at week 9 duloxetine was statistically significantly superior to placebo for reducing the experience of pain for only one of the six parameters measured.
 - The second study concluded that duloxetine significantly reduced the severity of overall pain, compared with placebo, at weeks 2-5 only. Severity of shoulder pain and time in pain whilst awake were only significantly reduced compared with placebo during weeks 1 and 2.
- Lundbeck therefore argued that this evidence was inadequate to support the claim that Cymbalta is effective in treating pain.
- Lundbeck discussed in detail each of the studies cited by ELA in its appeal, stating that for each study the evidence was inadequate to support the claim. The cited studies are at best exploratory and require more studies to provide conclusive evidence of efficacy.
- One study concluded *“Based upon the currently available evidence, the marketing of duloxetine as an antidepressant with analgesic properties for people with depression does not appear to be adequately supported.”*

Breach of Section 9.2.1 and 9.4

- The Cymbalta media release is not educational, it is promotional.
- The media release mirrors the marketing messages that are currently being promoted to healthcare professionals.
- This is part of a concerted effort by ELA/BI to convince healthcare professionals and the general public that Cymbalta is the new treatment for the 'physical symptoms' of MDD, an allegedly unmet need.
- The media release is promotional and breaches section 9.2.1 and 9.4 of the Code.
- Musculoskeletal pain is actually a common side effect of Cymbalta.
- The press release encourages a member of the general public to seek a prescription for Cymbalta.

Conclusion

- The Appeals Committee should uphold all the findings of the Code of Conduct Committee and the sanctions imposed.
- ELA/BI should be directed to withdraw all current marketing materials promoting the use of Cymbalta in the treatment of physical symptoms of depression and instructed not to promote Cymbalta for the physical symptoms of depression based on the evidence presented by ELA/BI in the course of this appeal in any future promotional material.

The Eli Lilly Australia representatives made the following comments in response to the Lundbeck presentation:

- The Chairman invited ELA to comment on the paragraph in the media release which refers to the dual action of Cymbalta and its efficacy in the physical symptoms and whether it was promotional. ELA responded that the Code permits at the time of product launch a media release can be issued which includes information about how a medicine works - this is a statement of fact.
- The TGA synthesised 6 papers and included reference to pain and physical symptoms in the PI.
- The Appeals Committee should place more weight on the TGA and the PI rather than a competitor's arguments.
- ELA did not ignore the advice by MA.
- ELA endeavoured to make available information that was educational and non-promotional.
- Lundbeck's own material makes reference to physical symptoms of depression.

The Chairman thanked representatives from both companies for their presentations and asked that they leave the meeting to allow the Committee to deliberate on the matters before them.

The Committee referred to the Code glossary for the definition of 'promote' and 'promotion' and the provisions pertaining to media releases. The Committee also reviewed the Cymbalta PI and noted statements in relation to pain or physical symptoms as were discussed in the appeal and particularly the reference to bodily pain as measured by the VAS.

The Committee noted that the approved dose of Cymbalta in Australia is 60mg daily. The four studies, for which additional measures in the evaluation of efficacy of duloxetine were examined, referred to in the clinical trials section of the PI, used doses of 60mg - 120mg daily, which is higher than the approved dose. The Committee considered that this information in the PI provided no evidence of the size of the effect in the additional measures (which included the bodily pain as measured by the VAS), except that the effect was positive. Further, the dose relevant to these findings was not specified. The Committee considered that this was inadequate evidence on which to base a claim of efficacy of Cymbalta in the treatment of pain or the physical symptoms associated with major depressive disorder. Antidepressants, and in particular dual action anti-depressants, are useful in the management of neuropathic pain, which is an uncommon pain disorder and which does not equate to the pain that is experienced widely in the community as a consequence of musculo-skeletal problems, such as joint and back pain. With the exception of neuropathic pain there is no evidence that Cymbalta has a direct analgesic effect.

It was not a question of Cymbalta having been promoted for the relief of pain generally, but rather that the media release was seen as promoting it for the relief of physical symptoms associated with MDD such as back and joint pain.

In the media release it was stated:

"Cymbalta works on the two neurological pathways, serotonin and noradrenaline, to treat not only the emotional symptoms of depression, but also the less acknowledged physical symptoms."

The implication of this statement is that the dual action of Cymbalta equates to a dual action in terms of treating both depression and physical symptoms. The Committee did not consider this was correct. Members considered there was undue emphasis in the media release on the treatment of physical symptoms associated with MDD, especially considering that these physical symptoms are not a core criterion for the diagnosis of MDD but are merely associated features.

Commonly people with depression can be preoccupied with physical symptoms such as pain, which is likely to improve if the depression is treated. But this does not indicate that antidepressant drug treatment has any direct effect on the physical symptoms or has an analgesic effect in pain. The Committee noted the use of antidepressants at low doses for neuropathic pain where there does appear to be a direct effect on neuropathic pain.

The Committee noted that ELA relied heavily on the statement in the Cymbalta PI, referenced above, to support the statements in the media release. The Committee did not consider that the PI statement could be interpreted as providing sufficient evidence to support the claim that Cymbalta was effective in treating the physical symptoms or musculo-skeletal pain associated with depression. Members determined that the statements in the media release to the general public went beyond what could be claimed from the PI and the clinical evidence. While it could be accepted that the media release did have an educational aspect, members were of the view that it was not balanced.

In relation to the alleged breaches of Sections 9.2.1 and 9.4 of the Code, the Appeals Committee agreed that the media release conveyed positive attributes of Cymbalta in relation to its efficacy in depression and the physical symptoms such as back and joint pain which may encourage a member of the public to seek a prescription for the product. The Appeals Committee was not persuaded that the Code Committee had erred in its reasoning or its finding and agreed with the Code Committee's determination that the media release was promoting a prescription medicine to the general public.

In a majority decision the Committee confirmed a breach of Sections 1.3 and 1.3.1 of the Code and in a unanimous decision confirmed a breach of Sections 9.2.1 and 9.4 of the Code.

Sanctions

Having not upheld the appeal the Appeals Committee reviewed the sanctions imposed by the Code of Conduct Committee. The Committee discussed the fine at length. A minority of members, who were of the view that there was no breach of Sections 1.3 and 1.3.1, considered that the fine should be reduced. However the majority of members determined that the penalty imposed by the Code Committee should remain.

In a majority decision the Committee determined that ELA should:

- Withdraw the media release from further use, including removal from all websites over which ELA has control.
- Pay a fine of \$100,000.

Exelon 982

Subject Company: Novartis Pharmaceuticals (Novartis)

Complainant: Lundbeck Australia

Product: Exelon

Complaint:

Lundbeck alleged that the media release issued by Novartis on 25 June 2008 did not provide a balanced overview of the tolerability of the patch as has been observed in the sole study that has investigated its use. Lundbeck stated its concern regarding the inclusion of data from medical journals to substantiate claims in material intended issued to the general public. These data are not readily accessible by the general public, who are unlikely to be able to assess the quality of such scientific data.

Lundbeck alleged that the media release provided an unbalanced and overwhelmingly positive impression of the tolerability of the patch, based on a misrepresentation of the tolerability results from the study, which was promoting the patch to the general public.

Sections of the Code:

Materials alleged to be in breach of the following Section of the Code:

- 9.2.1 Product specific media statements
- 9.2.3 Product specific media statements
- 9.4 Promotion to the general public

Response:

Novartis denied that it had breached the Code and argued that it was inappropriate and inaccurate to consider individual phrases in the media release in isolation. Novartis considered that the media release does not exceed what is permitted under the Code.

Novartis stated that the media release was written in a balanced way that reflected current community standards and was informative about a new delivery option for Exelon. Novartis also disagreed with the assertion that clinical papers and Product Information (PI) are not accessible by the general public as they can be easily found on the internet or patients can ask their doctor for them.

Code Committee determination

- In a majority decision the Committee found a breach of Sections 9.2.1 and 9.4 of the Code.
- In a unanimous decision the Committee found no breach of Section 9.2.3 of the Code.

Sanction

- In a majority decision pay a fine of \$15,000.

Consideration of the complaint

The Committee noted that it is difficult to issue a media release in relation to a specific prescription medicine without including information on the positive attributes and therefore becoming promotional. However members reiterated that the Code requires that a company must ensure any statement issued to the general public cannot be promotional. Members also acknowledged that Australian citizens had a right to know that a medicine was available or PBS listed.

Members were of the view that while most statements in the media release may be correct and consistent with the Product Information, there was an inappropriate emphasis on the reportedly fewer gastrointestinal side effects but no mention that serious side effects occurred more commonly with the patch than the capsules and more frequently led to early discontinuation of treatment. The Committee was of the view that the media release was selective in its communication about tolerability of the patch, which may lead a patient or carer to seek the 'new treatment with fewer side effects'. The Committee considered that the media release was promoting the medicine to the general public and was not sufficiently balanced with respect to its tolerability.

Members also commented that it was acceptable to state that it was a new delivery system for ameliorating the symptoms of Alzheimer's disease, there was insufficient evidence to support the claim that Exelon had the potential for improved outcomes in patients with this condition. The Committee was of the view that the public could access published papers through the internet and medical libraries; however a company must not make claims in information published for the general public, including media releases to the general public.

In a majority decision the Committee found the media release to be in breach of Sections 9.2.1 and 9.4 of the Code. In a unanimous decision the Committee found no breach of Section 9.2.3 of the Code.

In relation to the assertion by Novartis that the complaint bordered on being vexatious, the Committee determined that there was no reason for Lundbeck to be required to show cause why it should not be found in breach of Section 12.3 of the Code

Sanction

Having found several breaches of the Code the Committee considered what sanction should be imposed.

In a majority decision the Committee determined that Novartis should:

- Pay a fine of \$15,000.