CASE AUTH/2218/3/09

VOLUNTARY ADMISSION BY ASTRAZENECA

Promotion of Nexium

AstraZeneca voluntarily submitted that its promotion of Nexium 40mg (esomeprazole) was inconsistent with Section 4.2 of the Nexium summary of characteristics (SPC). In support of its submission AstraZeneca cited a Nexium detail aid and two independently produced treatment pathways distributed by the company.

AstraZeneca explained that during a review of its Nexium campaign it was considered that some materials did not take into account the entire wording in Section 4.2 of the SPC for the 40mg dose.

Section 4.1 of the Nexium SPC included the indication:
'Gastro-Oesophageal Reflux Disease
- **treatment of erosive reflux oesophagitis**
- **long-term management of patients with healed oesophagitis to prevent relapse**
- **symptomatic treatment of gastro-oesophageal reflux disease.'**

AstraZeneca's promotion was in line with this but in Section 4.2 of the SPC a distinction was made between the doses used for the different subsets of GORD:

'Gastro-Oesophageal Reflux Disease (GORD)
- **<u>treatment of erosive reflux oesophagitis</u>**
  40mg once daily for 4 weeks.

- **<u>long-term management of patients with healed oesophagitis to prevent relapse</u>**
  20mg once daily.

- **<u>symptomatic treatment of gastro-oesophageal reflux disease</u>**
  20mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated.'

GORD encompassed a spectrum of disorders from erosive oesophagitis to symptomatic disease without oesophagitis, from severe to mild.

AstraZeneca's interpretation of Section 4.2 was that the 40mg dose was only indicated in GORD patients who had a specific diagnosis of oesophagitis. When the licence was filed in 2000, oesophagitis was normally diagnosed by upper gastro-endoscopy albeit with an appreciation of a move to the current practice of a more symptomatic based approach.

In the promotional materials at issue the 40mg Nexium dose was promoted for all unresolved GORD, unresponsive to first line proton pump inhibitor (PPI) therapy. Unresolved GORD encompassed patients with or without oesophagitis.
- **Specifically, in the detail aid 40mg Nexium was positioned for reflux oesophagitis but also for symptomatic treatment in GORD (which, by implication, could include patients who might or might not have oesophagitis).**
- **In addition, two sets of independently produced local treatment guidelines for GORD, distributed by AstraZeneca, positioned Nexium 40mg for patients with unresolved GORD who had not responded to a four week course of a generic PPI. The guidelines referred to GORD patients (including those with or without oesophagitis) with no distinction made on the appropriate dose.**

AstraZeneca considered the material to be in breach of the Code; however, it believed that the error was made in good faith and noted the following:-

- **GORD was an ill defined term that was often misused in practice with other terms referring to gastro-intestinal pathology.**
- **During the initial assessment of the Nexium filing in 2000, the regulatory agencies questioned the value of upper gastro-endoscopy in the diagnosis and management of GORD and decided that the clinician should ultimately make this decision. This led to endoscopy not being mandatory prior to treatment with Nexium.**
- **International leading gastroenterologists had produced two sets of guidelines for the management of GORD in the past 10 years which questioned the value of subjecting GORD patients to an endoscopy and proposed empiric treatment with a PPI.**
- **The National Institute for health and Clinical Excellence (NICE) recommended that routine endoscopic evaluation of patients was not necessary and instead recommended empiric treatment with PPIs for reflux type dyspepsia (further confusing terminology).**
- **The materials were subject to close and considered scrutiny by senior medical personnel at AstraZeneca. Their opinion was that the materials were consistent with accepted clinical practice but, nevertheless, could be interpreted as not fully consistent with the licence.**

National and international guidelines and routine clinical practice recognised that GORD (with or without oesophagitis) might be managed without routine endoscopic evaluation favouring instead a symptomatic diagnosis for the GORD spectrum.

Despite the potential for ambiguity in its materials vis-à-vis the wording on the licence and current clinical practice, AstraZeneca believed it was appropriate to take this conservative view and accordingly all relevant promotional material for Nexium ceased on 25 February 2009 while clinical discussions were carried out. New materials would take account of the full wording of the license.

The detailed response from AstraZeneca is given below.

The Authority's Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potential serious breach of the Code or if the company failed to take appropriate action to address the matter. Promotion that was inconsistent with the SPC was a potentially serious matter and the Director thus decided that the admission must be treated as a complaint.

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The Panel noted that GORD encompassed a spectrum of disorders ranging from symptoms of acid reflux only without oesophagitis to erosive reflux oesophagitis where the stomach acid had damaged the lining of the oesophagus.

The Panel noted that in the Nexium SPC GORD was subdivided into treatment of erosive reflux oesophagitis (40mg once daily – an additional 4 weeks of treatment was recommended for patients in whom oesophagitis had not healed or who had persistent symptoms); long-term management of patients with healed oesophagitis to prevent relapses (20mg once daily) and symptomatic treatment of GORD (20mg once daily in patients without oesophagitis). If symptom control was not achieved after 4 weeks the patient should be further investigated. Once symptoms had resolved subsequent symptom control could be achieved using 20mg once daily. The Panel considered that before treatment with 40mg Nexium could begin, patients had to have a diagnosis of erosive reflux oesophagitis.

The Panel noted AstraZeneca's submission that Nexium 40mg was indicated, *inter alia*, for symptomatic treatment of GORD in patients whose symptoms were not controlled after 4 weeks on 20mg once daily. The Panel noted the SPC stated that such patients should be further investigated after 4 weeks but did not refer to the 40mg dose. The Panel considered the SPC meant that further clinical investigation was required at 4 weeks. This did not necessarily preclude the subsequent administration of the 40mg dose in those patients in whom a diagnosis of erosive reflux oesophagitis was made at 4 weeks.

The Panel noted AstraZeneca's submission that the diagnosis and management of GORD had evolved since the original Nexium regulatory filing in 2000. Current clinical practice generally relied on a symptomatic diagnosis for the GORD spectrum, rather than endoscopic diagnosis. The Panel noted the recommendations and evolving use of clinical terms by various national and international guidelines. AstraZeneca referred to an ambiguity in its materials vis-à-vis the wording on the licence and current clinical practice. The Panel noted that irrespective of current clinical practice promotional material must be in accordance with the medicine's marketing authorization and must not be inconsistent with the particulars listed in its SPC.

The Panel noted the detail aid at issue was entitled 'Unresolved GORD corrodes peoples lives' included bar charts headed 'Reducing symptom frequency' and 'Reducing heartburn severity' respectively beneath the heading 'Nexium 40mg provides a solution for patients with unresolved GORD by …'. The Panel noted that patients with unresolved GORD might or might not have oesophagitis. Nexium 40mg was indicated for treatment of erosive reflux oesophagitis. The Panel considered that the detail aid was thus inconsistent with the particulars listed in the Nexium SPC as admitted by AstraZeneca. A breach of the Code was ruled.

The Panel noted that the two sets of guidelines had each been independently developed and subsequently distributed by AstraZeneca. Each bore prescribing information for Nexium 20-40mg. Each guideline referred to second line treatment with Nexium 40mg for patients with unresolved reflux-type dyspepsia. It was thus not sufficiently clear that a diagnosis of erosive reflux oesophagitis was needed before 40mg therapy could begin. The guidelines were thus inconsistent with the particulars listed in the Nexium SPC as admitted by AstraZeneca. A breach of the Code was ruled in relation to each document.

AstraZeneca voluntarily submitted that its promotion of Nexium 40mg (esomeprazole) was inconsistent with Section 4.2 of the Nexium summary of characteristics (SPC). In support of its submission AstraZeneca cited a Nexium detail aid and two independently produced treatment pathways distributed by the company.

COMPLAINT

AstraZeneca explained that during a review of its campaign material it was queried whether the proposed positioning of the 40mg dose of Nexium for gastro-oesophageal reflux disease (GORD) was in line with the SPC. This led to an internal review of existing Nexium materials. The majority of materials were found to be consistent with the licensing particulars, however, in AstraZeneca's view certain materials did not take into account the entire wording in Section 4.2 of the SPC for the 40mg dose.

Licensing particulars

Section 4.1 of the Nexium SPC included the indication:
'Gastro-Oesophageal Reflux Disease
- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease.'

AstraZeneca's promotion was in line with this indication, however, within Section 4.2 of the SPC a distinction was made between the doses used for the different subsets of GORD:

'Gastro-Oesophageal Reflux Disease (GORD)
- treatment of erosive reflux oesophagitis
  40mg once daily for 4 weeks.

- long-term management of patients with healed oesophagitis to prevent relapse
  20mg once daily.

- symptomatic treatment of gastro-oesophageal reflux disease
  20mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated.'

The term GORD encompassed a spectrum of disorders which ranged from erosive oesophagitis to symptomatic disease without oesophagitis, from severe to mild.

AstraZeneca's interpretation of Section 4.2 was that the 40mg dose was only indicated in GORD patients who had a specific diagnosis of oesophagitis. At the time of filing for a licence in 2000, oesophagitis was normally diagnosed by upper gastro-endoscopy albeit with an appreciation of a move to the current practice of a more symptomatic based approach.

Promotional materials

In the promotional materials at issue the 40mg Nexium dose was promoted for all unresolved GORD, unresponsive to first line generic proton pump inhibitor (PPI) therapy. Unresolved GORD encompassed those patients with or without oesophagitis.

- Specifically, in the detail aid 40mg Nexium was positioned for reflux oesophagitis but also for symptomatic treatment in GORD (which, by implication, could include patients who might or might not have oesophagitis).
- In addition, two sets of independently produced local treatment guidelines for GORD were distributed by AstraZeneca. These guidelines positioned Nexium 40mg for patients with unresolved GORD who had not responded to a four week course of a generic PPI. The guidelines referred to GORD patients (including patients with or without oesophagitis) with no distinction made on the appropriate dose.

AstraZeneca judgement

AstraZeneca considered the material to be in breach of Clause 3.2; however, it believed that no other section of the Code was breached and that the error was made in good faith.

In particular, AstraZeneca noted the following:-

- GORD was an ill defined term that was often misused in practice with other terms referring to gastro-intestinal pathology.
- During the initial assessment of the Nexium filing in 2000, the regulatory agencies questioned the value of upper gastro-endoscopy in the diagnosis and management of GORD and decided that the clinician should ultimately make this decision. This led to endoscopy not being mandatory prior to treatment with Nexium.
- International leading gastroenterologists had produced two sets of guidelines for the management of GORD in the past 10 years. These guidelines questioned the value of subjecting GORD patients to an endoscopy and proposed empiric treatment with a PPI.
- The National Institute for health and Clinical Excellence (NICE) recommended that routine endoscopic evaluation of patients was not necessary and instead recommended empiric treatment with PPIs for reflux type dyspepsia (further confusing terminology).
- The materials were subject to close and considered scrutiny by senior medical personnel at AstraZeneca. Their opinion was that the materials were consistent with accepted clinical practice but, nevertheless, could be interpreted as not fully consistent with the licence.

National and international guidelines and routine clinical practice recognised that clinicians might decide to manage GORD (with or without oesophagitis) without the need for routine endoscopic evaluation and current practice favoured a symptomatic diagnosis for the GORD spectrum rather than an endoscopic intervention.

Despite the potential for ambiguity in its materials vis-à-vis the wording on the licence and current clinical practice, AstraZeneca believed it was appropriate to take this conservative view and accordingly all relevant promotional material for Nexium ceased on 25 February 2009 while clinical discussions were carried out. New materials would take account of the full wording of the license.

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Paragraph 5.4 of the Authority's Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potential serious breach of the Code or if the

company failed to take appropriate action to address the matter. Promotion that was inconsistent with the SPC was a potentially serious matter and the Director thus decided that the admission must be treated as a complaint.

AstraZeneca was asked to comment in relation to Clause 3.2 of the Code.

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RESPONSE

AstraZeneca provided further information about Nexium and GORD.

Nexium SPC and explanation of terms within the indications and posology section

In normal circumstances, the lower oesophageal sphincter at the top of the stomach prevented stomach acid from passing back into the oesophagus. There were a number of reasons for this to fail. Repeated reflux of acid into the lower oesophagus gave rise to GORD. The term GORD encompassed a spectrum of disorders that ranged from symptoms of acid reflux only to erosive reflux oesophagitis, where the stomach acid had damaged the lining of the oesophagus.

AstraZeneca reiterated the licensed indications as set out in the Nexium SPC.

The SPC, like other PPI SPCs did not state that endoscopy was required before commencing therapy with Nexium. Erosive reflux oesophagitis (RO) and RO were both classified using the Los-Angeles grading system. Any patient graded A-D was included in trials assessing the effectiveness of Nexium 40mg for RO. When these key phase III trials were published, they referred to these patients as having either RO or erosive RO therefore erosive RO and RO were used interchangeably, although reflux oesophagitis was a more accepted clinical term. It was noted that the latest international consensus publication recommended the use of RO over erosive RO as the latter was now an outdated term.

AstraZeneca interpreted Section 4.2 of the SPC to mean that 40mg Nexium was indicated in GORD patients who had a diagnosis of reflux oesophagitis and in GORD patients in whom an initial four-week course of Nexium 20mg had not provided sufficient response where further investigation was recommended.

The evolution of the diagnosis and management of GORD and RO

The management of GORD had varied and attempts had been made to standardise approaches to its management.

In 1999 the Genval guidelines were the first attempt to standardise management of GORD. Thirty-five doctors from 16 counties assessed the evidence for the diagnosis and treatment of patients with GORD: The group offered a definition of GORD and stated that endoscopy was thought to be of limited use in the routine management of most patients who presented with reflux symptoms and no alarm symptoms (symptoms that suggested a diagnosis of cancer). Empirical treatment was proposed as a first line of therapy.

In 2000 AstraZeneca obtained a licence for Nexium 20 and 40mg tablets for *inter alia* treatment of GORD, during the assessment process there was a reflection that the diagnosis of GORD might be made clinically without the need for endoscopy and that the treating clinician should ultimately make the decision.

In 2004, NICE issued guidelines for the management of dyspepsia in adults in primary care and recommended endoscopy and treatment with PPIs for patients with (reflux like) dyspepsia and GORD (including RO).

NICE advocated empirical therapy with PPIs for reflux type dyspepsia ie the types of patients that would present and likely to be clinically diagnosed with GORD. NICE also recommended that routine endoscopic evaluation of most patients was not necessary, rather, a list of alarm symptoms identified patients that would be suitable for referral. NICE also stated that early endoscopy had not demonstrated better patient outcomes than empirical treatment and that test and endoscopy had not been demonstrated to produce better patient outcomes than empirical treatment. The associated impact on patient safety was also assessed when making these recommendations.

Hence NICE supported empirical treatment with PPIs and reserved endoscopic evaluation to a limited group of patients identified at highest risk of other significant pathology.

To support clinical diagnosis of GORD a number of symptom-based questionnaires had been developed and validated for use, these included the reflux disease questionnaire (RDQ), GORD impact scale (GIS), ReQuest and GERD-Q.

In 2006, 44 experts from 18 countries produced the Montreal classification and definition of GORD. It defined GORD as a condition which developed when the reflux of stomach contents caused troublesome symptoms and/or complications. It also recommended the term reflux oesophagitis was used in preference to erosive oesophagitis.

In summary, GORD (including RO) could be diagnosed by endoscopy or clinically based on a symptomatic approach. NICE recommended the use of empiric therapy with PPIs rather than endoscopic evaluation for most patients.

Nexium materials and claims

The internal review revealed that the Nexium

detail aid, and the two sets of guidelines positioned Nexium 40mg for the treatment of GORD. However in AstraZeneca's view these materials were not sufficiently clear about whether patients referred to had reflux oesophagitis and did not provide advice to refer patients for investigation in line with the wording in the licence. AstraZeneca submitted that its positioning reflected clinical practice but did not take into account the full wording of the licence and that it should have advised further investigation in those patients with symptomatic GORD when considering escalating treatment to 40mg Nexium or use in RO.

Nexium detail aid (NEX12765a)

This detail aid was used between August 2007 to February 2009 and positioned Nexium for uncontrolled GORD; such positioning was covered by the licence. On page 6 Nexium 40mg was referred to in a meta-analysis assessing healing rates in patients with RO, again such use was covered within the scope of the licence. On pages 7 and 11, a trial called RESPONSE (then data on file but now published) was referred to showing how Nexium 40mg provided a solution for patients with unresolved GORD. In this trial patients were included if they had been diagnosed with GORD (and it was not clear which of these patients had been diagnosed with reflux oesophagitis or further investigated) and had unresolved symptoms despite 8 weeks' treatment with a full dose of another PPI. Upon entry into the trial patients were assigned to 8 weeks of treatment with Nexium 40mg. Page 12 again referred to Nexium's superiority for healing RO consistent with the information presented on page 6. Therefore although Nexium 40mg had been positioned for the treatment of RO in the detail aid it had also been positioned for the treatment of GORD where it was not clear which patients did or did not have RO or should be further investigated.

The two sets of guidelines had been developed independently of AstraZeneca; the company was given permission to distribute them in September 2007 and October 2008 respectively. These local treatment pathways had positioned Nexium as second line treatment for patients with suspected GORD. Nexium 40mg was positioned for those patients who had not had their GORD symptoms resolved after an initial trial with a generic PPI. However, again it was not clear whether these GORD patients would have RO or should be further investigated after their trial with generic PPI. Therefore AstraZeneca felt it inappropriate to distribute these guidelines and ceased this activity in February 2009.

Although clinical practice for GORD had evolved over the last 20 years, these materials had only been in use since August 2007 when it was considered that the materials would be in line with current clinical practice. Previous materials positioned Nexium 40mg for patients with RO. The review of AstraZeneca's internal materials was conducted in February 2009 when all current promotional activity for Nexium was also ceased.

Thus although these three promotional pieces were in line with current clinical practice and supported the clinical diagnosis of GORD, there were aspects in these pieces that did not extend to diagnosing RO or recommending further investigation before initiating treatment with Nexium 40mg. Thus, it in AstraZeneca's view these pieces were not strictly in line with the licensing particulars of Nexium and were in breach of Clause 3.2.

PANEL RULING

The Panel noted that GORD encompassed a spectrum of disorders ranging from symptoms of acid reflux only without oesophagitis to erosive reflux oesophagitis where the stomach acid had damaged the lining of the oesophagus.

The Panel noted that in the Nexium SPC GORD was subdivided into treatment of erosive reflux oesophagitis (40mg once daily – an additional 4 weeks of treatment was recommended for patients in whom oesophagitis had not healed or who had persistent symptoms); long-term management of patients with healed oesophagitis to prevent relapses (20mg once daily) and symptomatic treatment of GORD (20mg once daily in patients without oesophagitis). If symptom control was not achieved after 4 weeks the patient should be further investigated. Once symptoms had resolved subsequent symptom control could be achieved using 20mg once daily. The Panel considered that before treatment with 40mg Nexium could begin, patients had to have a diagnosis of erosive reflux oesophagitis.

The Panel noted AstraZeneca's submission that Nexium 40mg was indicated, *inter alia*, for symptomatic treatment of GORD in patients whose symptoms were not controlled after 4 weeks on 20mg once daily. The Panel noted the SPC stated that such patients should be further investigated after 4 weeks but did not refer to the 40mg dose. The Panel considered the SPC meant that further clinical investigation was required at 4 weeks. This did not necessarily preclude the subsequent administration of the 40mg dose in those patients in whom a diagnosis of erosive reflux oesophagitis was made at 4 weeks.

The Panel noted AstraZeneca's submission that the diagnosis and management of GORD had evolved since the original Nexium regulatory filing in 2000. Current clinical practice generally relied on a symptomatic diagnosis for the GORD spectrum, rather than endoscopic diagnosis. The Panel noted the recommendations and evolving use of clinical terms by the Genval guidelines, NICE and the Montreal classification. AstraZeneca referred to an ambiguity in its materials vis-à-vis

the wording on the licence and current clinical practice. The Panel noted that irrespective of current clinical practice promotional material must be in accordance with the medicine's marketing authorization and must not be inconsistent with the particulars listed in its SPC.

The Panel noted the detail aid at issue was entitled 'Unresolved GORD corrodes peoples lives'. Page 7 featured two bar charts headed 'Reducing symptom frequency' and 'Reducing heartburn severity' respectively beneath the heading 'Nexium 40mg provides a solution for patients with unresolved GORD by …'. The Panel noted that identical data also appeared on page 13 of the detail aid rather than page 11 referred to by AstraZeneca. The Panel noted that patients with unresolved GORD might or might not have oesophagitis. Nexium 40mg was indicated for treatment of erosive reflux oesophagitis. The Panel considered that pages 7 and 13 of the detail aid were thus inconsistent with the particulars listed in the Nexium SPC as admitted by AstraZeneca. A breach of Clause 3.2 was ruled.

The Panel noted that the two sets of guidelines had each been independently developed and subsequently distributed by AstraZeneca. Each bore prescribing information for Nexium 20-40mg. Each guideline referred to second line treatment with Nexium 40mg for patients with unresolved reflux-type dyspepsia. It was thus not sufficiently clear that a diagnosis of erosive reflux oesophagitis was needed before 40 mg therapy could begin. The guidelines were thus inconsistent with the particulars listed in the Nexium SPC as admitted by AstraZeneca. A breach of Clause 3.2 was ruled in relation to each document.

Proceeding commenced 18 March 2009

Case completed 24 April 2009