CASES AUTH/2394/3/11 and AUTH/2395/3/11

BOEHRINGER INGELHEIM v LUNDBECK and TEVA

Promotion of Azilect

Boehringer Ingelheim complained about joint activities undertaken by Lundbeck and Teva at a World Parkinson's congress to support Azilect (rasagiline). The congress was attended by health professionals and patients.

The detailed responses from Lundbeck and Teva are given below.

Boehringer Ingelheim noted that all delegate bags, including those of patients, contained an invitation to a Lundbeck/Teva satellite symposium entitled 'Slowing disease progression in Parkinson's disease' which in Boehringer Ingelheim's view implied that attendees would hear about a medicine to slow Parkinson's disease. The evidence on which this claim was made was the Attenuation of Disease Progression with Azilect Given Once Daily (ADAGIO) study (Olanow *et al* 2009).

Boehringer Ingelheim alleged that the invitation in effect promoted Azilect in a manner which was not in accordance with the terms of its marketing authorization; Azilect was not licensed to slow disease progression. Furthermore the ADAGIO study included a 2mg dose which was not licensed. The claim 'slowing disease progression' did not fairly represent the ADAGIO study and in that regard was misleading, could not be substantiated and did not encourage the rational use of Azilect. High standards had not been maintained and the special nature of medicines had not been recognised. Boehringer Ingelheim further alleged that the invitation had been distributed to the public who had thus been exposed to promotional messages for a prescription only medicine which might raise unfounded hopes of successful treatment.

The Panel noted that the symposium at issue consisted of three short presentations, 'The ADAGIO trial – key results, facts and misperceptions', 'Translating clinical study results into clinical practice and treatment guidelines' and 'The emerging algorithm for earlier (pre-motor) diagnosis of Parkinson's disease'. Although neither Azilect nor rasagiline were referred to on the invitation, some health professionals might nonetheless make the link between the ADAGIO study, the results of which had been published in September 2009, and Azilect. The ADAGIO study examined the possibility that Azilect had disease-modifying effects. Azilect was not licensed to slow Parkinson's disease progression.

The supplementary information to the Code stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited. The Panel did not know what was said at the symposium nor had it seen the ADAGIO study presentation; the complaint was only about the invitation.

The Panel did not consider that it was necessarily unacceptable to discuss the results of ADAGIO within a *bona fide* scientific symposium which met the supplementary information to the Code. There was no complaint before the Panel on this point. The Panel did not consider that it had been established that the invitation, as included in the health professionals' delegate bags, promoted Azilect to slow Parkinson's disease progression. No breach of the Code was ruled. The Panel considered that the statement 'Slowing disease progression in Parkinson's disease', as stated on the invitation, could be seen as aspirational and noted Lundbeck and Teva's submission that it was intended to reflect the whole meeting content. The Panel did not consider that the statement was misleading with regard to the outcome of the ADAGIO study or that it exaggerated the properties of Azilect and did not encourage rational use of the medicine. No breach of the Code was ruled.

The Panel noted that invitations had also been put in all of the delegate bags for patients/carers attending the congress. This should not have happened. The Panel did not consider, however, that the invitation was an advertisement for Azilect and in that regard it ruled no breach of the Code. Nonetheless the Panel considered that although patients/carers would not have been able to attend the symposium, the invitation was, in itself, enough for at least some of them to link Azilect with the slowing of disease progression in Parkinson's disease. In that regard the Panel considered that the invitation might encourage some patients to ask their prescribers to prescribe Azilect and that it also had the potential to raise unfounded hopes of successful treatment. A breach of the Code was ruled. The inclusion of the invitation in patients'/carers' delegate bags meant that high standards had not been maintained. A further breach of the Code was ruled.

The Panel did not consider that giving the invitation to patients/carers meant that the special nature of medicines had not been recognised. No breach of the Code was ruled. The Panel did not consider that the invitation was promotional material *per se* and in that regard no breach was ruled.

The Panel noted it's rulings of breaches of the Code above and considered that, *de facto*, not all applicable codes had been complied with. A breach of the Code was ruled.

The Panel noted that Boehringer Ingelheim had alleged a breach of that part of the Code which dealt with relationships with patient organisations. The Panel did not consider that the matter was covered by that part of the Code and thus ruled no breach.

Boehringer Ingelheim alleged that the presentation of results from the ADAGIO Study on an exhibition stand misrepresented the data and promoted Azilect for an unlicensed indication (ie to slow the clinical progression of Parkinson's disease). The claim Slowing clinical progression' was not substantiated by the ADAGIO data and did not encourage the rational use of Azilect. High standards had not been maintained.

The Panel noted that Azilect was licensed for the treatment of idiopathic Parkinson's disease as monotherapy, or with levodopa, at a dose of 1mg/day. Claims for Azilect on the exhibition stand referred to 'delayed clinical progression', 'slowing the clinical progression' and 'reduction in clinical progression'. Azilect was not authorized to slow clinical progression in Parkinson's disease. In that regard the Panel considered that the claims at issue were inconsistent with the particulars listed in the Azilect SPC and did not encourage the rational use of Azilect. Breaches of the Code were ruled.

The Panel noted that the claims for delayed disease progression were derived from the ADAGIO study. The ADAGIO study showed that early treatment with Azilect 1mg/day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with Azilect 2mg/day did not. The authors concluded that given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had disease modifying effects. The Panel thus considered that the claims at issue did not reflect the findings of the ADAGIO study and were misleading in that regard. The claims could not be substantiated by reference to the ADAGIO study. High standards had not been maintained. Breaches of the Code were ruled which were upheld on appeal.

Boehringer Ingelheim noted that visitors to the exhibition stand were encouraged, via a business card, to visit the website Mypdinfo.com which contained a guide to Parkinson's disease medicines. Boehringer Ingelheim noted that some medicines were mentioned but other, similar ones, were not. The section on medicines like Azilect stated that they were being investigated for slowing disease progression. The information provided was not a balanced view of UK therapies, it was not accurate or up-to-date and might raise unfounded hopes of successful treatment.

The Panel noted that a business card referring readers to the Mypdinfo website had been distributed from the Lundbeck/Teva exhibition stand. Neither the business card nor the website content had been approved for use in the UK; it appeared that it had been distributed by a non-UK company representative. Lundbeck and Teva acknowledged that they were responsible for the activities of other country affiliates and both companies had reinforced to global colleagues that activities taking place in the UK must conform with the UK Code.

The Panel noted that a document which could be downloaded from the website detailed dopamine agonists and although it was stated that ropinirole and rotigotine could be administered once daily it was not stated that pramipexole was also available in a once daily formulation. In that regard the Panel did not consider that the website gave a balanced, accurate and up-to-date overview of treatment options in the UK. A breach of the Code was ruled as alleged. The document also detailed MAO-B inhibitors and stated that rasagiline and seligiline were being investigated for their potential to slow disease progression. The Panel noted its comments above about the ADAGIO study and considered that the statement might encourage some members of the public to ask for either one of those specific medicines and raise unfounded hope of successful treatment. A breach of Code was ruled.

With regard to the section detailing future medicines, the Panel noted that the website contained the statement that 'recently published findings for the MAO-B inhibitor, rasagiline (Azilect), suggest that it could slow the progression of PD'. The Panel noted its comments above and considered that the statement did not accurately reflect the results of the ADAGIO study and was misleading in that regard. In the Panel's view, a statement that a medicine *could* produce a result, rarely negated the impression that it *would* produce that result. The Panel considered that the statement was unbalanced and would give patients/carers unfounded hope of successful treatment. Breaches of the Code were ruled.

Boehringer Ingelheim Limited complained about joint activities undertaken by Lundbeck Ltd and Teva Pharmaceuticals Ltd at the 2nd World Parkinson's Congress (WPC) in Glasgow, 22 September to 1 October 2010, to support Azilect (rasagiline), a medicine which they co-promoted for the treatment of Parkinson's disease. Boehringer Ingelheim stated that according to the congress organisers, patients comprised 20% of the approximately 3,600 delegates.

A Invitation to a pre-congress educational course entitled 'Slowing disease progression in Parkinson's disease'

The invitation (ref UK/AZI/1009/0030) was included in all delegate bags, including those of patients.

COMPLAINT

In Boehringer Ingelheim's view, 'Slowing disease progression in Parkinson's disease' implied that attendees would hear about a Parkinson's therapy that would slow progression of Parkinson's disease. The evidence on which this claim was made was the Attenuation of Disease Progression with Azilect Given Once Daily (ADAGIO) study (Olanow *et al* 2009).

The European Medicines Evaluation Agency (EMEA, now the European Medicines Agency, EMA) guideline on clinical investigation of medicines in Parkinson's disease required that to make a claim for disease modification, two criteria must be met: firstly, a demonstrated significant delay in clinical measures of disease progression; secondly, a quantifiable effect on the underlying pathophysiological process eg by biochemical markers or neuroimaging measures which correlated to a meaningful and persistent change in clinical function.

The ADAGIO study design did not address or meet the requirements of the EMEA guideline.

The ADAGIO study stated that early-start treatment with rasagiline 1mg/day met all end points in the primary analysis: a smaller mean (±SE) increase (which represented a worsening of the condition) in the unified Parkinson's disease rating scale (UPDRS) score between weeks 12 and 36 (0.09±0.02 points/week in the early-start group vs 0.14±0.01 points/week in the placebo group, p=0.01), a smaller increase in the score between baseline and week 72 (2.82±0.53 points in the early-start group vs 4.52±0.56 points in the delayed-start group, p=0.02), and non inferiority between the two groups with respect to the rate of change in the UPDRS score between weeks 48 and 72 (0.085±0.02 points/week in the early-start group vs 0.085±0.02 points/week in the delayed-start group, p<0.001). None of the three end points were met with rasagiline 2mg/day, since the change in the UPDRS score between baseline and week 72 was not significantly different in the two groups (3.47±0.50 points in the early start group and 3.11±0.50 points in the delayed-start group, p=0.60).

The authors concluded that early treatment with rasagiline 1mg/day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with rasagiline 2mg/day did not. Because the two doses were associated with different outcomes, the authors stated that the study results must be interpreted with caution.

There was general consensus among experts that no medicine had adequately demonstrated neuroprotection or disease modification in Parkinson's disease patients.

The lack of widely accepted clinical or brain imaging criteria for disease-modification and the lack of diagnostic markers to monitor the effects of a treatment intervention in very early disease remained important hurdles to overcome.

Boehringer Ingelheim alleged that the nature of the invitation – the title of the session, the presentation titles and the fact that the invitation was inserted into all delegate bags including those of patients, breached the following clauses of the 2008 Code:

- 3.2 – promotion of a medicine in accordance with the terms of its marketing authorization, in that Azilect was not licenced to slow disease progression and was clearly the product discussed in the satellite symposium. Furthermore, the ADAGIO study, which was the topic of the first presentation, studied two doses, including a 2mg dose for which there was no marketing authorization.

- 7.2 – the claim was not accurate, balanced, fair or objective. It was misleading in the presentation of the ADAGIO study results, which did not meet its primary endpoint for both doses studied.

- 7.4 – the claim 'Slowing disease progression' could not be substantiated using the EMA criteria in the ADAGIO study design, or from Olanow *et al*.

- 7.10 – the claim of 'Slowing disease progression' did not encourage the rational use of Azilect by presenting it objectively and without exaggerating its properties.

- 9.1 – by exposing patients to the claim 'Slowing disease progression' in the invitation, high standards had not been maintained.

- 9.2 – exposing patients to the claim 'Slowing disease progression' did not recognise the special nature of medicines.

- 11.1 - the public were invited to a satellite symposium designed for health professionals and exposed to promotional messages for a prescription only medicine.

- 22.1 – the invitation advertised a prescription only medicine to the public. Azilect was the only product for Parkinson's disease jointly marketed by Teva and Lundbeck and the subject of the ADAGIO study, data from which was presented in the satellite symposium.

- 22.2 – the invitation did not present information to patients in a factual or balanced way. It might raise unfounded hopes of successful treatment with rasagiline.

Boehringer Ingelheim was concerned by the tone and content of inter-company correspondence on the matter as, in summary, Lundbeck and Teva considered that there was no breach of the Code because Azilect was not mentioned by name in the invitation and that they were not responsible for the distribution of the invitation in the delegate bags by the congress organisers.

Under Clause 1.3, the term medicine meant any branded or unbranded medicine intended for use in humans which required a marketing authorization. Avoidance of use of a brand name was not a defence; previous cases had demonstrated that companies were responsible for materials and activities where there was sufficient information provided to identify the product (eg Case AUTH/1873/8/06). Boehringer Ingelheim considered that in the invitation, use of the Lundbeck and Teva corporate logos and reference to the ADAGIO study was sufficient to identify that the product was Azilect.

Under Clause 1.1, UK pharmaceutical companies were responsible for activities undertaken by other country affiliates or corporate head offices in the UK, events at which UK clinicians were present and activities and events at which UK patients were present. Sponsorship of scientific meetings was specifically referred to in Clause 1.2.

Under Clauses 1.7, 20 and 23 of the 2008 Code, UK pharmaceutical companies were responsible for ensuring that patient organisations, consultants and third parties (agencies, congress organisers and the like) were aware of the Code and the responsibilities associated with compliance in connection with materials and activities conducted in the UK, or at events where UK clinicians and patients were present. Boehringer Ingelheim alleged that inclusion of the invitation in the delegate bag advertised a prescription only medicine to the patient/members of the public attendees, in breach of Clauses 22.1, 1.7, 20 and 23.

RESPONSE

Lundbeck and Teva submitted a joint response and stated that the invitation was for a scientific satellite symposium, organised and Continuing Medical Educational (CME) accredited by the congress and supported by an unrestricted educational grant from Teva and Lundbeck (as stated on the invitation) corporate departments. The invitation was designed by corporate colleagues and approved in the UK. The symposium was part of an educational day that preceded the main congress and, as such, was intended for health professionals only. This was confirmed on the congress website which stated:

> 'Pre-congress educational course #1
> Scientific Course Tuesday, September 28, 2010
>
> Note: as per UK pharmaceutical code, these sessions in Course #1 will be open only to healthcare professionals due to the nature of the talks and specific drug treatments that will be discussed. All courses have been designed by the WPC leadership.'

Patients attending the congress would be expected to arrive the following day. In supporting the meeting, Teva and Lundbeck expected that the congress organisers would distribute the invitation only to health professionals via the delegate bags. Lundbeck and Teva did not have control over the actual distribution of the invitation and it appeared they were also included in the patient delegate bags. This should not have happened and both companies had reviewed this incident and would ensure this issue was addressed for any future meetings. Due to the timing of the meeting it was, however, unlikely that any patients would have been at the conference during the meeting. Furthermore, health professionals and patients had different conference identity badges which were checked on entry to the meeting to ensure only health professionals were permitted access.

The invitation did not refer to Azilect nor did it contain any promotional claims for rasagiline. It was an invitation to a non-promotional educational meeting and outlined the presentation topics. The title of the meeting was intended to reflect the whole meeting content as a wide ranging discussion of 'Slowing disease progression in Parkinson's disease' as an important research and therapeutic goal in Parkinson's disease. This was in keeping with the educational nature and organisation of the meeting rather than focussing simply on the effects of medicines or indeed the promotion of rasagiline. In support of this, only the first of the three presentations featured a specific clinical study (a double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study)) which was very reasonable given that this was recently published in the New England Journal of Medicine and evaluated one of the EMA's key parameters for a disease modifying effect (referred to by Boehringer Ingelheim), namely an effect on clinical disease progression. Such studies were notoriously difficult to conduct, were few in number and this one, which included rasagiline, was a high profile publication in the Parkinson's disease academic community which merited inclusion in any current discussion around the role of medicines on disease progression.

Lundbeck and Teva noted that they had sponsored this pre-congress educational course via an unrestricted educational grant in association with the congress as an educational meeting for health professionals and not as a promotional meeting for rasagiline. As this was not a promotional meeting for rasagiline and the invitation did not contain any promotional claims for the product; the companies did not accept the alleged breaches of Clauses 3.2, 7.2, 7.4, 7.10, 9.1, 9.2, 11.1, 22.1 and 22.2.

The companies did accept that, due to the unanticipated distribution process of the conference organisers, invitations had been put into patient delegate bags. As mentioned, the conference organisers were clear that only health professionals were to attend the symposium, and the event took place before patient activities commenced.

Teva and Lundbeck therefore did not accept that the invitation in question promoted rasagiline.

PANEL RULING

The Panel noted that the invitation at issue was to a satellite symposium held as part of a formal pre-congress educational course. The title of the symposium was 'Slowing disease progression in Parkinson's disease'. The symposium consisted of three short presentations, 'The ADAGIO trial – key results, facts and misperceptions', 'Translating clinical study results into clinical practice and treatment guidelines' and 'The emerging algorithm for earlier (pre-motor) diagnosis of Parkinson's disease'. The Panel accepted that although neither Azilect nor rasagiline were referred to on the invitation, some health professionals might nonetheless make the link between the ADAGIO study, the results of which had

been published in the New England Journal of Medicine in September 2009, and Azilect. The ADAGIO study examined the possibility that Azilect had disease-modifying effects. Azilect was not licensed to slow Parkinson's disease progression.

The Panel noted that the supplementary information to Clause 3, Marketing Authorization, stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under Clause 3 or any other clause. The Panel did not know what was said at the symposium nor had it seen the ADAGIO study presentation; the complaint was only about the invitation.

The Panel did not consider that it was necessarily unacceptable to discuss the results of ADAGIO within a *bona fide* scientific symposium which met the supplementary information to Clause 3. There was no complaint before the Panel on this point. The Panel did not consider that it had been established that the invitation, as included in the health professionals' delegate bags, promoted Azilect to slow Parkinson's disease progression. No breach of Clause 3.2 was ruled. The Panel considered that the statement 'Slowing disease progression in Parkinson's disease', as stated on the invitation, could be seen as aspirational and noted Lundbeck and Teva's submission that it was intended to reflect the whole meeting content. The Panel did not consider that the statement was misleading with regard to the outcome of the ADAGIO study. No breach of Clause 7.2 was ruled. The Panel also ruled no breach of Clause 7.4. The Panel did not consider that the statement exaggerated the properties of Azilect and did not encourage rational use of the medicine. No breach of Clause 7.10 was ruled.

The Panel noted that invitations had also been put in all of the delegate bags for patients/carers attending the congress. This should not have happened. The Panel did not consider, however, that the invitation was an advertisement for Azilect and in that regard it ruled no breach of Clause 22.1. Nonetheless the Panel considered that although patients/carers would not have been able to attend the symposium, the invitation was, in itself, enough for at least some of them to link Azilect with the slowing of disease progression in Parkinson's disease. In that regard the Panel considered that the invitation might encourage some patients to ask their prescribers to prescribe Azilect and that it also had the potential to raise unfounded hopes of successful treatment. A breach of Clause 22.2 was ruled. The inclusion of the invitation in patients'/carers' delegate bags meant that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel did not consider that giving the invitation to patients/carers meant that the special nature of medicines had not been recognised. No breach of Clause 9.2 was ruled. The Panel did not consider that the invitation was promotional material *per se* and in that regard there could be no breach of Clause 11.1. The Panel ruled accordingly.

The Panel noted it's rulings of breaches of the Code above and considered that, *de facto*, not all applicable codes had been complied with. A breach of Clause 1.7 was ruled.

The Panel noted that Boehringer Ingelheim had alleged a breach of Clause 23. Clause 23 set out the requirements for the relationships between pharmaceutical companies and patient organisations. The Panel did not consider that the matter was covered by Clause 23 which dealt in the main with issues of transparency. Materials distributed to patients was covered by Clause 22. The Panel thus ruled no breach of Clause 23.

B The presentation of results from the ADAGIO study on an exhibition stand

COMPLAINT

Boehringer Ingelheim alleged that the exhibition stand used a moving visual image/slide show which misrepresented the ADAGIO data. Statements on the exhibition stand, referenced to Olanow *et al*, included:

'delivers the dual benefit of delayed clinical progression with improved symptomatic control in Parkinson's disease'

'the only treatment to demonstrate slowing the clinical progression and symptomatic efficacy in PD in a prospective delayed start study'

'provides patients with 38% reduction in clinical progression at 72 weeks'

Boehringer Ingelheim alleged that the claims were in breach of the following clauses of the 2008 Code:

- 3.2 – promotion of a medicine in accordance with the terms of its marketing authorization, in that Azilect was not licenced to slow clinical progression; the 2mg dose reported in the ADAGIO study, the results of which did not reach statistical significance, has no marketing authorization for the treatment of Parkinson's disease or for slowing disease progression.

- 7.2 – the claim 'Slowing clinical progression' was not accurate, balanced, fair or objective. It was misleading in the presentation of the ADAGIO study results, which did not meet its primary endpoint for both doses studied.

- 7.4 – the claim 'Slowing clinical progression' was not substantiated by Olanow *et al*.

- 7.10 – the claim 'Slowing clinical progression' did not encourage the rational use of Azilect by presenting it objectively and without exaggerating its properties.

- 9.1 – by presenting the ADAGIO data in this way, high standards had not been maintained.

Boehringer Ingelheim was concerned by the tone and content of inter-company correspondence on the matter as Lundbeck and Teva considered that because they did not actively promote 2mg rasagiline, the use of the ADAGIO study in promotional material and activities was acceptable.

Reference to the ADAGIO study on the exhibition stand, drew health professionals' attention to the study results, the study design and the inclusion of a 2mg rasagiline arm. In Case AUTH/2263/9/09 the Panel considered that, given the inclusion of an unlicensed dosing regimen in the ArTEN study, the advertisement at issue in effect constituted promotion that was inconsistent with the particulars listed in the summary of product characteristics (SPC) in breach of Clause 3.2. Boehringer Ingelheim alleged that the promotional messages based on ADAGIO results displayed on the exhibition stand constituted promotion that was inconsistent with the particulars listed in the Azilect SPC in breach of Clause 3.2.

The ADAGIO study results claimed 38% less clinical progression for the early start arm compared with the delayed start arm. The authors stated that the clinical significance of this difference, which reflected a difference of 1.7 UPDRS points between the early start and delayed start groups that received rasagiline 1mg/day was not known.

RESPONSE

Lundbeck and Teva noted that in Point A above, Boehringer Ingelheim had cited the EMA guideline on investigation of medicines for Parkinson's disease which stated that to demonstrate disease modification on Parkinson's disease a medicine must demonstrate a significant delay in clinical measures of disease progression and an effect on the underlying pathophysiology of the disease (eg biomarkers or neuroimaging measures). Boehringer Ingelheim appeared to have confused disease modification with slowing clinical progression. The EMA guidelines drew a clear distinction between them. All the companies' communications about ADAGIO were restricted to objective presentation of the demonstrated effect on clinical progression that was achieved by treating earlier with rasagiline vs delaying treatment for 36 weeks. In addition, they highlighted other symptomatic benefits of treatment with rasagiline, in accordance with the marketing authorization. Both these treatment approaches used 1mg rasagiline and clearly fell within the EU indication.

The companies had also included a personal testimony from a key opinion leader in Parkinson's disease who was additionally one of the main investigators in the ADAGIO study. This testimony further illustrated a clinician's perspective on the difference between agents which might influence disease modification and those which might affect clinical progression.

The ADAGIO study demonstrated a significant delay in clinical progression for rasagiline 1mg as the second part of its hierarchical Primary Endpoint (table 2; page 1274; -1.68 ± 0.75, p=0.02, also referred to was figure 3A, page 1275 for graphical representation). In essence, the group who started with 1mg rasagiline monotherapy (as per the current EU licence) at the beginning of the study had a significant delay to their clinical disease progression compared with those who started 1mg rasagiline monotherapy (as per the current EU licence) 36 weeks later. This result addressed the first criterion of the EMA guideline. Biomarkers or neuroimaging were not investigated in the ADAGIO study. None of the claims cited by Boehringer Ingelheim discussed disease modification. All claims only referred to the effects on clinical progression that were demonstrated by 'within licence' use of rasagiline 1mg in the ADAGIO study. These two were distinct and separate phenomena within the EMA guideline. Additionally, rasagiline 2mg was not a licensed dose anywhere in the world and was therefore not discussed in promotional materials.

Lundbeck and Teva noted that all patients who received 1mg rasagiline in the ADAGIO study were eligible for treatment according to the terms of the current Azilect marketing authorization. With respect to the current promotion of Azilect, the results from the 2mg rasagiline arm of the study could be considered irrelevant as this dose was not licensed anywhere in the world and all promotional use of the ADAGIO study referred only to data which were within the scope of the present marketing authorization.

It was not unusual for clinical studies to produce results that were difficult to interpret, particularly in relation to dose and clinical response. The ADAGIO authors proposed a number of explanations for the differing rasagiline 1mg and 2mg study arm results. This remained a well designed and conducted clinical study and the results for the 1mg rasagiline arm on clinical progression were scientifically robust and not invalidated by the fact that the 2mg rasagiline arm did not show a similar outcome.

With regard to Clause 3.2, Lundbeck and Teva noted that the Azilect marketing authorization included the indication for treatment of Parkinson's disease as monotherapy. ADAGIO assessed the impact on clinical progression of starting monotherapy immediately after diagnosis vs starting monotherapy 36 weeks later. This comparison of Parkinson's disease treatment strategy demonstrated a significant difference in symptom progression by 72 weeks as part of the study's primary outcome ie treating early was advantageous over delaying treatment. Both treatment approaches, and therefore this result, were in accordance with the terms of the marketing authorization.

With regard to Clauses 7.2, 7.4 and 7.10, Lundbeck and Teva noted, as detailed above, that ADAGIO demonstrated that rasagiline slowed clinical progression as part of its primary endpoint in a

delayed start study design. Substantiation was Table 2; page 1274; -1.68 ± 0.75, p=0.02. The absolute values for UPDRS deterioration by 72 weeks were given in the same table (4.5 delayed start vs 2.8 early start ie 38% reduction in this measure of clinical progression when rasagiline was started early). With regard to Clause 7.2, Lundbeck and Teva noted that rasagiline 2mg was not a licensed dose anywhere in the world and was therefore not discussed in promotional materials. With regard to Clause 7.10 the companies noted that the claim was objective and without exaggeration.

With regard to Clause 9.1, Lundbeck and Teva submitted that Boehringer Ingelheim appeared to have confused disease modification with slowing clinical progression. As previously discussed, the EMA guidelines drew a clear distinction between them. The companies restricted their communications about ADAGIO to objective presentation of the demonstrated effect on clinical progression that was achieved by treating earlier with rasagiline vs delaying treatment for 36 weeks. Both these treatment approaches which used 1mg rasagiline clearly fell within the EU indication. High standards had been maintained.

PANEL RULING

The Panel noted that Azilect was licensed for the treatment of idiopathic Parkinson's disease as monotherapy, or with levodopa, at a dose of 1mg/day. Claims for Azilect on the exhibition stand referred to 'delayed clinical progression', 'slowing the clinical progression' and 'reduction in clinical progression'. Azilect was not authorized to slow clinical progression in Parkinson's disease. In that regard the Panel considered that the claims at issue were inconsistent with the particulars listed in the Azilect SPC. A breach of Clause 3.2 was ruled. The Panel considered that the claims did not encourage the rational use of Azilect. A breach of Clause 7.10 was ruled.

The Panel noted that the claims for delayed disease progression were derived from the ADAGIO study. The ADAGIO study showed that early treatment with Azilect 1mg/day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with Azilect 2mg/day did not. The authors concluded that given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had disease modifying effects. The Panel thus considered that the claims at issue did not reflect the findings of the ADAGIO study and were misleading in that regard. A breach of Clause 7.2 was ruled. The claims could not be substantiated by reference to Olanow *et al* (the ADAGIO study). A breach of Clause 7.4 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

All of the Panel's rulings in Point B were appealed.

APPEAL BY TEVA and LUNDBECK

Teva and Lundbeck noted that the Panel's ruling concluded that Azilect was not authorized to slow clinical progression in Parkinson's disease. In that regard the Panel considered that the claims at issue were inconsistent with the particulars listed in the Azilect SPC. The claims at issue in the ruling were: '… delivers dual benefit of **delayed clinical progression** with improved symptomatic control in Parkinson's disease', '… the only treatment to demonstrate **slowing the clinical progression** and symptomatic efficacy in PD in a prospective delayed study' and '… provides patients with 38% **reduction in clinical progression** at 72 weeks' (emphasis added).

Parkinson's disease was a progressive neurodegenerative disease whose initial clinical features resulted from the loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain. The definition of Parkinson's disease was rather difficult. Diagnosing Parkinson's disease first required identifying parkinsonism (a syndrome characterised by rigidity, tremor and bradykinesia), loss of pigmented dopaminergic neurons in the brain stem (particularly in the pars compacta region of the substantia nigra) and the presence of neuronal intracytoplasmic inclusions called Lewy bodies.

There were currently no validated biomarkers established for Parkinson's disease. In theory, therefore, definitive diagnosis of Parkinson's disease required a post-mortem neuropathological examination. However, patient history and examination by skilled clinicians could establish the diagnosis with fairly high certainty; even today, the diagnosis of Parkinson's disease was based on clinical features and progress was monitored by clinical tools (the UPDRS being the most established). The UPDRS measured symptom burden at a point in time but when used serially over time it provided a measure of disease progression.

The slides used in the exhibition stand used the words 'clinical progression' rather than 'disease modification'. The key opinion leader's personal testimony set out definitions of 'clinical progression' and 'disease modification'. As he explained, the terms 'affecting clinical progression', 'slowing clinical progression' and 'delaying clinical progression' all implied a change in the clinical manifestations (symptoms and/or signs) of the syndrome but did not necessarily imply any change in the underlying disease process and, in fact, it was not possible to establish conclusively disease modifying effect of any intervention given the current understanding of Parkinson's disease, not least due to the lack of validated biomarkers and neuroimaging techniques.

The companies submitted that the EMA guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease clearly distinguished between disease progression and disease modification: 'If a delay in disease progression is shown, this does not imply that a new agent is also a disease modifier'. The above definition of disease

progression did not imply disease modification, ie changing the course of the underlying disease process. However, as these two terms sounded very similar they could lead to confusion among health professionals (even more so among those who were more engaged in the clinic and less in academia). Therefore, to avoid such confusion and present matters with more clarity, the companies had used 'clinical progression' instead of 'disease progression' in their materials to accurately reflect the simple observation of clinical UPDRS over time without any implication as to an effect on the underlying pathology.

Azilect was indicated for the treatment of idiopathic Parkinson's disease as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations. Some of the data referenced in Azilect's SPC (specifically study 1 in Section 5.1) examined the efficacy of Azilect by reference to statistically significant differences in UPDRS scores. Such data, self-evidently, supported Azilect's licensed therapeutic indication for the monotherapy of idiopathic Parkinson's disease. The slowing of clinical progression claims at issue here were also evidenced by a statistically significant difference in UPDRS scores (discussed in more detail below), showing the consistency of such claims with the SPC.

Based on the SPC (monotherapy for the treatment of Parkinson's disease), treatment goals in Parkinson's disease (symptom control) and the previously discussed meaning of 'clinical progression' (worsening of symptoms), the companies submitted that the claims 'slowing clinical progression', 'delayed clinical progression' and 'reduction in clinical progression' were not inconsistent with the SPC. On these grounds, the companies did not accept that the ruling of a breach of Clause 3.2 was justified.

Furthermore, on the basis of the above in relation to the consistency of the claims at issue with the SPC, the companies disagreed that the claims did not encourage the rational use of Azilect. The companies therefore denied a breach of Clause 7.10.

In its ruling about the ADAGIO study the Panel 'noted that the claims for **delayed disease progression** were derived from the ADAGIO study. The ADAGIO study showed that early treatment with Azilect 1mg/day provided benefits that were consistent with a possible **disease-modifying effect**, but early treatment with Azilect 2mg/day did not. The authors concluded that given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had **disease modifying effects**. The Panel thus considered that the claims at issue did not reflect the findings of the ADAGIO study and were misleading in that regard' (emphasis added). The claims at issue were those referred to above.

The companies noted the reference in the first sentence above to 'claims for delayed disease progression'. The claims at issue all referred to clinical progression, not disease progression. The term 'clinical progression', was used with intention to clarify that the symptomatic effect was present not just at a single time point, but lasted for the duration of the study, thereby producing a statistically significant reduction/delay/slowing in clinical progression. The ADAGIO study was designed to examine the possibility that Azilect had a disease modifying effect in Parkinson's disease. It produced robust and very useful data and demonstrated the clinical benefit of early treatment with Azilect. The ADAGIO study demonstrated a statistically significant delay in clinical progression for Azilect 1mg as the second part of its hierarchical primary endpoint (p=0.02). In essence, the group who started with Azilect 1mg monotherapy (as per the current EU licence) at the beginning of the study had a statistically significant delay to their clinical disease progression compared with those who started Azilect 1mg monotherapy (as per the current EU licence) 36 weeks later. These statistically significant data formed the basis of the claim that Azilect delayed clinical progression of Parkinson's disease. All claims only referred to the effects on clinical progression that were demonstrated by the licenced use of Azilect 1mg in the ADAGIO study.

Whilst Olanow *et al* stated that they 'cannot definitely conclude that rasagiline at a dose of 1mg per day has disease-modifying effects', this statement was an overall conclusion as to the hypothesis that rasagiline 1mg per day had disease-modifying effects. This statement did not, however, mean that it could not be said that rasagiline 1mg per day delayed clinical progression of Parkinson's disease on the basis of statistically significant data from the ADAGIO study.

On this basis, the companies disagreed with the Panel's ruling that the claims were misleading and in breach of Clause 7.2. Furthermore, it was clear that the claims could be substantiated by Olanow *et al* and therefore did not breach Clause 7.4.

The companies noted that in relation to its rulings above, the Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. The companies submitted that in considering whether or not high standards had been maintained, attention must be paid to the supplementary information to Clause 9.1, which listed a number of examples of situations where high standards had not been maintained eg the provision of private prescription forms pre-printed with the name of a medicine. The above set out in detail why the companies submitted that the claims at issue did not breach the Code. Whatever the Appeal Board's ruling, it was clear from the supplementary information to Clause 9.1 and previous Panel rulings on this clause that the claims made at an exhibition stand at the 2nd World Parkinson's Congress, were simply not the sort of claims in relation to which a ruling of a Clause 9.1 breach should be ruled. It was unreasonable and incorrect to place them in the same category as the promotional materials referred to in the supplementary information to Clause 9.1. The companies submitted that high standards were, by some margin, maintained throughout and thus denied a breach of Clause 9.1.

COMMENTS FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim had no further comments.

APPEAL BOARD RULING

The Appeal Board noted that the authors of the ADAGIO study stated that their study results must be interpreted with caution. Although the study showed that early treatment with Azilect 1mg/day provided benefits consistent with a possible disease-modifying effect, early treatment with Azilect 2mg/day did not. The authors concluded that given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had disease modifying effects.

The Appeal Board did not accept the companies' submission that the phrase 'clinical progression' in the video looped screen shots related to symptoms not 'disease modification'. All three screen shots were referenced to the ADAGIO study. The Appeal Board noted that the first screen shot stated 'Delivers the dual benefit of delayed clinical progression with improved symptomatic control in Parkinson's disease'. The Appeal Board considered that the implication was that the 'dual benefit' was 'delayed clinical progression' *and* 'improved symptomatic control'.

Similarly the second screen shot referred to 'slowing the clinical progression' and 'symptomatic efficacy'. The Appeal Board considered that by distinguishing between clinical progression and symptom control the material implied that clinical progression was in effect 'disease modification'. The Appeal Board considered that this implication was compounded by the third screen shot at issue which featured a bar chart that compared the mean UPDRS change from baseline for Azilect delayed-start vs Azilect early-start. The bar chart included the statement 'Data presented for the licensed dose only'. A statistically significant advantage for Azilect early-start was shown (p=0.02). At the top of the screen shot was the claim 'Provides patients with 38% reduction in clinical progression' at 72 weeks. However, the screen failed to convey the authors' conclusions that, given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had disease modifying effects.

The Appeal Board noted that Azilect 1mg/day was licensed for the treatment of idiopathic Parkinson's disease as monotherapy, or with levodopa. Azilect was not authorized to slow clinical progression in Parkinson's disease. The Appeal Board considered that the claims at issue were inconsistent with the particulars listed in the Azilect SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The Appeal Board considered that the claims did not encourage the rational use of Azilect. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.10. The appeal on both points was unsuccessful.

In addition, the Appeal Board considered that the claims at issue did not reflect the findings of the ADAGIO study and were misleading in that regard as alleged. The claims could not be substantiated by Olanow *et al* (the ADAGIO study). The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

C Link to Mypdinfo.com

COMPLAINT

Boehringer Ingelheim stated that visitors to the exhibition stand in the public area of the exhibition hall, including patients, were encouraged to follow a link to the website www.Mypdinfo.com, provided through a business card. The website contained a guide to Parkinson's disease medicines, available for download as a PDF. Under the section on dopamine agonists, once daily formulations of rotigotine and ropinirole were mentioned, but not pramipexole (Boehringer Ingelheim's product Mirapexin Prolonged Release, launched in the UK in October 2009). The section on monoamine oxidase-B (MAO-B) inhibitors [such as Azilect] stated that they were being investigated for slowing disease progression, but the same was not discussed for the dopamine agonists or pramipexole. This did not provide a balanced view of current available therapies for UK patients. Boehringer Ingelheim alleged breaches of Clause 7.2, in that the information was not accurate or up-to-date and Clause 22.2 in that the information presented might raise unfounded hopes of successful treatment.

Specifically, within the website section on future medicines the following information was given about slowing disease progression (last accessed by Boehringer Ingelheim 26 October 2010):

> 'One of the key research targets for Parkinson's disease (PD) is finding a way to stop the disorder developing and progressing – ie, finding a treatment to modify the disease course. However, this effect is difficult to measure in a clinical study, and it also requires many years of follow-up to confirm any outcomes.
>
> Despite these problems, several PD medications have been investigated in trials specifically designed to assess the rate of disease progression, and recently published findings for the MAO-B inhibitor, rasagiline (Azilect), suggest that it could slow the progression of PD. The dopamine agonist, pramipexole (Mirapexin), is also being investigated for this purpose, although study results are not yet available.
>
> Currently, no medication is approved/licensed for modifying PD progression, although this possibility remains an exciting prospect for the future.'

This statement did not reflect the current state of clinical research in regard to the publication of study results. Boehringer Ingelheim alleged breaches of Clauses 7.2 and 22.2.

Boehringer Ingelheim was concerned by the tone and content of inter-company correspondence on the matter as, in summary, Lundbeck and Teva considered that because the Mypdinfo.com was a European patient information site, with no links to UK affiliates of either company, they were not responsible.

The business card referring to the website was available from the Teva/Lundbeck exhibition stand in the public area of the exhibition hall, accessible to health professionals, patients and members of the public, including those from the UK. As Teva and Lundbeck were responsible under the Code for activities at this congress, Boehringer Ingelheim refuted their assertion that they did not direct UK health professionals or patients to the website.

RESPONSE

Lundbeck and Teva noted that Mypdinfo.com was a European patient information site with the content authored and provided by the European Parkinson's Disease Association (EPDA). The companies supported the website on a Europe-wide basis through non-UK company departments. Neither UK affiliate had any direct association with the support of this website and neither directed UK patients or health professionals to it. The companies did not dispute the existence of the business card with the website address and having reviewed those attending the meeting representing both companies and the related activities they concluded that the card in question was distributed by a non-UK company representative at the exhibition stand.

With regard to the quoted content from the website, it stated clearly that no medicines were currently approved/licensed for slowing disease progression in Parkinson's disease, although this possibility remained an exciting prospect for the future. The companies believed this was an accurate reflection of research in this area and consequently would not raise unfounded hopes of successful treatment amongst the public. They accepted that they were responsible for all activities undertaken by other country affiliates or corporate head offices in the UK. As such, all material distributed at the stand should have been approved under the Code. This did not happen with regard to the Mypdinfo.com business card and the actual site content. Both companies had therefore, as a matter of priority, reinforced to global company colleagues that all activities relating to international scientific meetings taking place in the UK must conform to the requirements of the Code.

PANEL RULING

The Panel noted that a business card referring readers to the Mypdinfo website had been distributed from the Lundbeck/Teva exhibition stand. Neither the business card nor the website content had been approved for use in the UK; it appeared that it had been distributed by a non-UK company representative. The Panel noted Lundbeck and Teva's acknowledgement that they were responsible for the activities of other country affiliates and that both companies had reinforced to global colleagues that activities taking place in the UK must conform with the UK Code. Lundbeck and Teva had not commented on the website content.

The Panel noted that a PDF document which could be downloaded from the website detailed dopamine agonists and although it was stated that ropinirole (ReQuip and ReQuip LP) and rotigotine (Neupro) could be administered once daily it was not stated that pramipexole (Mirapexin) was also available in a once daily formulation. In that regard the Panel did not consider that the website gave a balanced, accurate and up-to-date overview of treatment options in the UK. A breach of Clauses 7.2 was ruled as alleged. The PDF document also detailed MAO-B inhibitors and stated that rasagiline (Azilect) and seligiline (Eldepryl) were being investigated for their potential to slow disease progression. The Panel noted its comments above about the ADAGIO study and considered that the statement might encourage some members of the public to ask for either one of those specific medicines and raise unfounded hope of successful treatment. A breach of Clause 22.2 was ruled.

With regard to the section detailing future medicines, the Panel noted that the website contained the statement that 'recently published findings for the MAO-B inhibitor, rasagiline (Azilect), suggest that it could slow the progression of PD'. The Panel noted its comments at B above with regard to the ADAGIO study. The Panel considered that the statement did not accurately reflect the results of that study and was misleading in that regard. In the Panel's view, a statement that a medicine *could* produce a result, rarely negated the impression that it *would* produce that result. A breach of Clause 7.2 was ruled. The Panel considered that the statement was unbalanced and would give patients/carers unfounded hope of successful treatment. A breach of Clause 22.2 was ruled.

Complaint received	**17 March 2011**
Case completed	**12 July 2011**