CASE AUTH/3048/6/18

BIAL PHARMA v PROFILE PHARMA

Promotion of Xadago

Bial Pharma UK complained about material distributed from a promotional exhibition stand by Profile Pharma to support its promotion of Xadago (safinamide). Xadago was indicated as add-on therapy for adults with idiopathic Parkinson's disease. Bial marketed Ongentys (opicapone) which was indicated as adjunctive therapy in patients with Parkinson's disease.

The materials at issue were two study summaries: 'Opicapone as adjunct to levodopa therapy in patients with Parkinson's Disease and motor fluctuations' which detailed Lees *et al* (2017) (BIPARK II); and 'Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson's Disease and motor fluctuations: A randomised clinical trial' which detailed Schapira *et al* (2016) (SETTLE).

Bial stated that Ongentys and Xadago were indicated in similar patient populations but they had different mechanisms of action. Bial submitted that for Profile Pharma to selectively produce a standalone clinical trial summary of its competitor's product to use alongside summaries of clinical trials of its own product, and to distribute these as promotional materials, encouraged an indirect comparison of the two products where there were no direct comparative clinical studies.

Bial alleged that the summaries available on the exhibition stand did not provide a balanced summary of all of the available evidence and the selection of the summaries and the selective way they were written, was intended to indirectly favour Xadago over Ongentys.

The detailed response from Profile is given below.

The clinical trial summaries had been produced using PICO (population, intervention, comparator and outcome) methodology. The Panel noted the briefing document to support the use of the summaries stated that they were to be used by key account managers proactively with all relevant health professionals to support the formulary and market access of Xadago. The briefing stated that as there were no head-to-head trials, the summaries were a key tool to differentiate Xadago from other adjunct therapies.

It was clear to the Panel that the summaries would inevitably lead to comparisons of the products. This was not necessarily unacceptable, it was a question of whether the content of each summary was fair, whether health professionals were provided with an overview of all the data and if not, what was the basis of selection and was such selection fair.

The materials were used to promote Xadago. The document which detailed the Xadago study included prescribing information. It appeared from Profile's submission that a number of criteria were used when selecting the studies to be summarised, ie was the medicine one of the most relevant? was it a pivotal study? and was there data in order to present the summary using a PICO format? Profile stated that the PICO methodology would highlight differences in studies. Health professionals would use data from a number of sources in making decisions. In the Panel's view it was disingenuous to claim that material produced using similar methodology would not encourage health professionals to make comparisons. Profile's approach facilitated indirect comparisons.

The Panel noted Profile's submission that it had produced a summary on study 016 and if there were none available on the stand it might have been because it had run out. Profile submitted that it always sent equal quantities of the summaries. It appeared that Bial did not accept Profile's submission in this regard. The Panel noted that the PICO summaries briefing document listed study 016. The Panel considered all the circumstances and ruled that there was no breach of the Code in relation to the summary of study 016.

It was not clear to the Panel why one of the key papers referenced in the Xadago EPAR, study 018, had not been summarised because it failed to meet its primary endpoint. In the Panel's view this was an important study and the failure to reach its primary end point would be of interest. Profile stated that the two year study was of interest to health professionals as no other medicine in this therapy area had long-term data. The Panel further queried Profile's submission that the limitations of the methodology and hierarchical statistics were not easy to explain in the PICO format so it was not used as it would be misleading. It was not entirely clear to the Panel why study 018 could not be presented in this format or in an alternative format if necessary.

Overall the Panel did not consider that use of the material to make indirect comparisons was misleading as alleged. That the studies were separate and there was no direct comparison would be apparent from the use of individual documents. The Panel ruled no breach of the Code. However, the Panel was concerned that taking all the factors into account the absence of a summary for a pivitol study on Profile's product which did not meet its primary endpoint meant that the basis of selection was unfair and did not reflect all the evidence. A breach of the Code was ruled. This meant the indirect comparison was misleading and the Panel ruled a breach of the Code.

Bial Pharma UK Limited complained about material produced by Profile Pharma Ltd to support its promotion of Xadago (safinamide). Xadago was indicated as add-on therapy for adults with idiopathic Parkinson's disease. Bial marketed Ongentys (opicapone) which was indicated as adjunctive therapy in patients with Parkinson's disease.

The materials at issue were two study summaries: 'Opicapone as adjunct to levodopa therapy in patients with Parkinson's Disease and motor fluctuations' (ref UK_XAD_187) which detailed Lees *et al* (2017) (BIPARK II) and 'Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson's Disease and motor fluctuations: A randomised clinical trial' which detailed Schapira *et al* (2016) (SETTLE). The study summaries were distributed from Profile's stand at a promotional meeting.

COMPLAINT

Bial stated that although Ongentys and Xadago had different mechanisms of action, they were indicated in similar patient populations. The company submitted that for a pharmaceutical company to selectively produce a standalone clinical trial summary of its competitor's product, with the intention that the summary be used alongside summaries of clinical trials of its own product, and distribute these as promotional materials, could only have one purpose ie to encourage and/or facilitate health professionals and other decision makers to indirectly compare the two products.

Bial stated that the summaries available on the Profile stand were a selection of the pivotal studies of Ongentys and Xadago and as such did not provide a balanced summary of all of the available evidence. The selection of the summaries and the selective way they were written, was intended to favour Xadago over Ongentys in indirect comparisons.

Indirect comparisons

Bial stated that it was concerned that, in the absence of comparative studies, Profile had produced promotional materials in the form of individual clinical study summaries; these were distributed via the salesforce with the intention that it would directly or indirectly encourage health professionals and other decision makers to indirectly compare the efficacy and safety of Xadago and other competing products. In Bial's view, the only reason that a salesforce would be supplied with summaries of clinical trials of competitor products, as promotional items, would be to encourage or facilitate indirect comparisons between products.

Bial stated that its concerns about indirect comparisons fell into two areas:

1 The encouragement by Profile's salesforce (or otherwise) of indirect comparisons, by health professionals and other decision makers, between products where there were no direct comparative clinical studies. Bial noted that breaches of the Code had previously been ruled in relation to the use of indirect comparisons. In this instance:

a) Profile's view was that because the clinical study summaries used a recognised methodology, they could be distributed as standalone promotional items. In Bial's view, and in consideration of previous PMCPA cases, it was not acceptable for a company to encourage indirect comparisons between two competitive products. Bial alleged a breach of Clause 7.
b) During an inter-company meeting Profile stated that the materials were intended to be used to facilitate indirect comparisons by health professionals and other decision makers. Furthermore, in response to a request for clarification by Bial during the meeting, this statement was reiterated by Profile. Profile subsequently denied the statement had been made and as a result the minutes of the meeting had not been agreed. Based on Profile's statement on indirect comparisons made at the meeting, though subsequently retracted, Bial remained of the view that the study summaries were provided to the salesforce as promotional items simply for the purpose of encouraging indirect comparisons, in breach of the Code.
c) Profile had not otherwise explained why the study summaries were used as promotional items.

2 The study summaries and their availability at promotional and other meetings was selective, such that the data provided to health professionals to make indirect comparisons did not reflect all the available evidence, and the selection and the presentation of data appeared, by design, to favour Xadago.

a) At the promotional meeting at which the materials in question were obtained, there was no summary available from the Profile stand of the second pivotal study of Xadago in the licensed indication (Study 016). The size of the mean estimate of the improvement in the primary variable in this study was approximately 50% of the mean estimate of Schapira *et al*. Once again this appeared to be selective, failed to take account of all of the relevant clinical data of Xadago and was part of a deliberate strategy to bias any indirect comparison by health professionals of Xadago and Ongentys in favour of Xadago.
b) Although during inter-company dialogue, Profile indicated that an additional study summary (Study 016) had been produced, this was not available at the meeting in question. If this item was available, not making it available on the meetings stand could also be considered selective, as the summarised data would reflect Xadago in a less favourable light. As Bial had not seen this item, it relied on Profile's statement that the item was available.
c) As the study summaries were distributed as separate items, rather than bound together, selectivity in distribution was almost inevitable and had been shown to be established as practice by Profile as evidenced by the summaries available at the promotional

meeting at which these materials were obtained.

Bial stated that its fundamental concern was that the use of the materials would encourage health professionals and other decision makers to make indirect comparisons. The original selection of certain clinical studies, in this summarised form, without taking into account all of the available published data, was a concern. Profile's intention with these materials, and the indication that clear briefing materials were not initially considered, was a concern. Further, Bial's suggestion that all published and available clinical studies were provided in one bound document, to prevent any selective use in a promotional context by the salesforce, had been rejected by Profile, compounding Bial's concern that the study summaries were, by design, to be used selectively.

Bial alleged that this approach was in breach of Clause 7, particularly Clause 7.2 but equally a breach of Clause 7.3 could be argued.

RESPONSE

Profile explained that it produced a series of purely factual summaries of the key papers for the most used or newest medicines for Parkinson's patients in need of adjunct therapy to levodopa. It had not made any claims beyond presenting results. It had presented the results of the same endpoints where available and made clear where they were not published in the paper. The endpoints presented were those the European Medicines Agency (EMA) required for registration studies in Parkinson's disease. This was done in conjunction with experts in the therapy area to advise on the most relevant medicines and the pivotal studies for each. The studies were summarised using a PICO (population, intervention, comparator and outcome) methodology. The National Institute for Health and Care Excellence (NICE) guideline manual had endorsed this methodology which would highlight differences in studies. Profile did not make any comparisons nor direct its salesforce to make them. Profile provided the summaries as individual items and could not be responsible for how a decision maker used a purely factual summary of a clinical paper or even a full clinical paper. Profile's aim was to summarise the data as fairly and accurately as possible.

Profile noted Bial's accusation that Profile's intention of the materials was for its salesforce to make indirect comparisons with health professionals, yet no evidence of this was offered. Further, this point could be applied to a lot of promotional materials. Profile stated that its intention was to aid decision making through producing factual summaries with an established methodology, not to encourage indirect comparisons. Of course, health professionals made indirect comparisons daily when making prescribing decisions and so, if Bial's logic was accepted, all promotional material could be used to make indirect comparisons.

Profile categorically refuted Bial's version of what was said at the meeting and provided its version of the meeting minutes. Profile noted that Bial wrote up the minutes and that Profile corrected them in track change. Bial refused to accept the changes, even to remove its post meeting suppositions and factual errors. Profile stated that Bial rejected all of Profile's changes and made no attempt to reach an agreement.

Profile stated that without accepting that it intended indirect comparison to be made it would address how the materials might be in breach of the Code. Bial had not stated where in the Code indirect comparisons were not allowed. Profile accepted there were many limitations with an indirect comparison but Clause 7.3 did not prohibit them *per se* and therefore Bial's statement that by having an indirect comparison without further clarification Profile did not accept as being in breach.

Profile noted that Bial offered no evidence that Profile salesforce encouraged indirect comparisons. Bial did not cite particular PMCPA cases to substantiate that all indirect comparisons were in breach. The rulings in Case AUTH/2199/1/09 and Case AUTH/2778/8/15 related to indirect comparison where studies had different endpoints. This did not necessarily mean all indirect comparisons would be in breach of the Code. There were very few instances where head-to-head studies were available for all comparisons. In Cases AUTH/2440/10/11 and AUTH/2441/10/11 the Panel ruled that head-to-head studies were not needed to substantiate a claim for 'class-comparable efficacy'. The Panel considered 'comparable' meant that the two products were worthy of comparison or able to be compared. The Panel did not consider that comparability implied equivalence. This would indicate that in some circumstances comparisons without head-to-head studies ie an indirect comparison might be acceptable.

Profile noted that Bial alleged that the summaries only had one purpose ie to encourage indirect comparisons, without offering any evidence of this or considering that most promotional materials had many purposes.

Listing the requirements of Clause 7.3, Profile stated that an indirect comparison would not be in breach of the Code if, in effect, it met those requirements:

Profile reiterated that it did not make an indirect comparison but if the materials were to be used by a health professional or other decision maker for this purpose then none of the listed requirements of Clause 7.3 would have been breached.

Profile categorically refuted Bial's version of what was said during an inter-company meeting and noted that, in addition to the incorrect comment about indirect comparisons, there were many other errors in the minutes. Profile never stated that the intention was for indirect comparisons to be made. Profile submitted that it stated during the meeting that the PICO methodology was an accepted method for the basis of indirect comparisons as used by Cochrane, NICE and other decision makers precisely because it highlighted the differences in studies. This was totally misconstrued by Bial. The intention was to

summarise the key studies to facilitate decision making. The salesforce was not directed to make indirect comparisons and Profile only stated that it could not be responsible for health professionals making indirect comparisons as they must do this continually to make appropriate prescribing decisions, as there were rarely head-to-head studies to help them. Throughout the subsequent inter-company dialogue Bial refused to acknowledge that and continued to incorrectly state that Profile had stated the materials were intended to make indirect comparisons. The Code allowed comparisons as long as they complied with Clause 7.3 and Profile did not accept that it had breached Clause 7.3.

Profile considered that each summary was a balanced presentation of the key data in each paper. Only results were presented and no inferences or claims about the data were made. The choice of papers was such as to present a pivotal study or studies for each medicine. Profile stated that it ensured both its pivotal studies were summarised and that its choice of studies for other medicines represented the data for those medicines. Profile noted that Bial did not state how the data was not balanced or how the summaries and how they were written favoured Xadago. The Code did not prohibit the use of competitor data in promotion.

Profile noted that Bial refused to believe that Profile had summarised both of its pivotal studies namely study 016 and SETTLE. Bial did not find the summary for Study 016 so accused Profile of not having one and therefore 'cherry picking' its data. Bial would not accept Profile's explanation that if there were none on the stand maybe it was because it had run out as it was more popular. Profile stated that it always sent equal quantities of the summaries. As the meeting in question had not been identified, Profile could not confirm the exact quantities of the summaries provided. Profile provided copies of all of the summaries in the series.

Profile stated that it explained to Bial in the inter-company meeting, that rather than cherry picking data it had actually not summarised a key paper that was referenced in Xadago's European Public Assessment Report (EPAR) and summary of product characteristics (SPC), Study 018, as it failed to meet its primary endpoint. This was the results of a 2-year study, and as such was of interest to health professionals as no other medicine in this therapy area had long-term data. The limitations of the methodology and hierarchical statistics were not easy to explain in the PICO format so Profile did not present the data in that format because it considered that it would be misleading. A copy of the paper was provided. Bial then incorrectly stated that Profile was using data from a study in an unlicensed indication (Motion study in early Parkinson's disease), which apart from forming part of the reference safety information, Profile never used. Bial also incorrectly referred to its own pivotal phase III trial as a phase IV open label study.

Profile refuted that the summaries were written in a way that was selective, it had only summarised the papers for each medicine, provided the results for the same endpoints where possible and where the endpoints were different, made sure this was clear. There had been no cherry picking.
As for the summaries not presenting all the available evidence, Profile submitted that it was not feasible to produce summaries of all papers in this this area, nor would that be useful to prescribers and decision makers. The company took expert advice that the data presented was representative and not misleading. Profile did not set out to favour Xadago. The data was factual, if there were differences that were more favourable to one medicine over another then so be it. It was up to prescribers or decision makers to draw their own conclusions. Profile had not drawn any conclusions on any of the studies.

Profile noted Bial's request that the summaries be bound together but did not understand how this would remove the accusation of an indirect comparison. Conversely, Profile considered that binding them together made indirect comparisons more likely which was why it did not agree to it. Bial offered no evidence that the materials were used selectively to support its inflammatory comment 'established as practice'. Profile noted that, in the course of inter-company dialogue, it offered to brief the salesforce to make sure all summaries were available on promotional stands and to tell health professionals and decision makers of all the paper summaries available so they could choose which they wanted.

In conclusion Profile refuted any breach of Clause 7.2 or 7.3. Bial had not been clear in how Profile might have done that and what aspects of the materials breached each clause. Profile did not consider that all indirect comparisons would be in breach of the Code but accepted they had many limitations. For that very reason, Profile produced individual summaries of key papers for prescribers and decision makers in order to avoid bias. This was done to help those in the NHS as many formulary committees used the PICO methodology when reviewing papers.

PANEL RULING

The Panel noted the briefing document to support the use of the PICO key study leaflets stated that they were to be used by key account managers proactively with all relevant health professionals to support the formulary and market access of Xadago within the UK. The briefing stated that as there were no head-to-head trials, the PICO leaflets were a key tool to differentiate Xadago from other adjunct therapies. It further stated that the PICOs looked at each trial and compared using the following criteria: population, intervention comparison and outcome.

It was clear to the Panel that the summaries would inevitably lead to comparisons of the products. This was not necessarily unacceptable it was a question of whether the content of each summary was fair, whether health professionals were provided with an overview of all the data and if not, what was the basis of selection and was such selection fair.

The materials were used to promote Xadago. The document which detailed the Xadago study included prescribing information. It appeared from Profile's

submission that a number of criteria were used when selecting the studies to be summarised, firstly was the medicine one of the most relevant, secondly was the study a pivotal study and thirdly was there data in order to present the summary using a PICO format. Profile stated that the PICO methodology would highlight differences in studies. Health professionals would use data from a number of sources in making decisions. In the Panel's view it was disingenuous to claim that material produced using similar methodology would not encourage health professionals to make comparisons. Profile's approach facilitated indirect comparisons.

The Panel noted Profile's submission that it had produced a summary on study 016 and if there were none available on the stand it might have been because it had run out. Profile submitted that it always sent equal quantities of the summaries. It appeared that Bial did not accept Profile's submission in this regard. The Panel noted that the PICO summaries briefing document listed study 016. The Panel considered all the circumstances and ruled that there was no breach of Clause 7.2 and 7.3 in relation to the summary of study 016.

It was not clear to the Panel why one of the key papers referenced in the Xadago EPAR, study 018, had not been summarised because it failed to meet its primary endpoint. In the Panel's view this was an important study and the failure to reach its primary end point would be of interest. Profile stated that the two year study was of interest to health professionals as no other medicine in this therapy area had long-term data. The Panel further queried Profile's submission that the limitations of the methodology and hierarchical statistics were not easy to explain in the PICO format so it was not used as it would be misleading. The Panel noted that using the PICO format the data would be set out as population, intervention, comparator and outcome. It was not entirely clear to the Panel why study 018 could not be presented in this format or in an alternative format if necessary.

Overall the Panel did not consider that use of the material to make indirect comparisons was misleading as alleged. That the studies were separate and there was no direct comparison would be apparent from the use of individual documents. The Panel ruled no breach of Clauses 7.2 and 7.3. However, the Panel was concerned that taking all the factors into account the absence of a summary for a pivitol study on Profile's product which did not meet its primary endpoint meant that the basis of selection was unfair and did not reflect all the evidence. A breach of Clause 7.2 was ruled. This meant the indirect comparison was misleading and the Panel also ruled a breach of Clause 7.3.

Complaint received **7 June 2018**

Case completed **10 October 2018**