CASE/0261/08/24 *NO BREACH OF THE CODE*

COMPLAINANT v BIAL

Allegation regarding prescribing information

CASE SUMMARY

This case was in relation to the prescribing information for Ongentys (opicapone) in which the complainant alleged there was a discrepancy with respect to the concomitant use of Ongentys with the MAO-B inhibitor safinamide.

The outcome under the 2021 Code was:

No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 5.1 (x2)	**Requirement to maintain high standards at all times**
No Breach of Clause 6.1	**Requirement that information/ claims/ comparisons must not be inaccurate or misleading**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint was received from an anonymous, contactable complainant about Bial.

COMPLAINT

The complaint wording is reproduced below with some typographical errors corrected:

> "I am writing to anonymously express my concern regarding inaccurate information provided by Bial.
>
> During a recent interaction, a Bial representative assured me that their product, opicapone, could be safely administered concomitantly with levodopa, carbidopa and safinamide in a patient experiencing motor fluctuations. However, upon reviewing the provided prescribing information, I found a statement indicating "there is no experience with opicapone when used concomitantly with the MAO-B inhibitor safinamide."
>
> This discrepancy is alarming given the existence of the OPTIPARK study, which included 67 patients taking opicapone and safinamide together, as published by

Reichmann et al. in 2020. Please note this study was led by the pharmaceutical company themselves.

I have attached a copy of the prescribing information webpage for your reference. It is important to note that their page includes multiple identification codes and repetitive disclaimers, making it challenging to navigate. [URL provided]

I believe this discrepancy in information represents a significant issue and could potentially lead to incorrect medication practices. Bial should investigate this matter promptly and provide accurate and up-to-date information to healthcare professionals."

In response to a request for further information from the Case Preparation Manager, the complainant provided the following information:

"I want to emphasise that I had a positive interaction with the Sales Representative and there are no concerns on that front. My complaint is specifically related to the accuracy and clarity of the prescribing information available on the company's website which I used to validate the information I had regarding opicapone and safinamide interaction.

The webpage is also difficult to navigate due to multiple identification codes and repetitive statements."

When writing to Bial, the PMCPA asked it to consider the requirements of Clauses 2, 5.1 and 6.1 of the 2021 Code.

BIAL'S RESPONSE

The response from Bial is reproduced below:

"First of all we want to highlight that Bial Pharma UK, although not a member of the Association of British Pharmaceutical Industry, has undertaken to strictly abide by the ABPI Code of Practice as well as all relevant laws and regulation. We have a strong sense of duty towards Patients, Healthcare Professionals, and Society and aim to maintain high standards at all times; therefore any allegation or concern is taken extremely seriously by Bial Pharma UK.

It is relieving for us to hear that the complainant had a positive interaction with the Bial sales representative and did not raise any concern on that front; we are pleased that the complainant has emphasized this in their second email, so that it is clear that our sales representatives have not fallen short of the expected standards of conduct in carrying out their duties. We note that the complaint received is related to the Ongentys (opicapone) Prescribing Information as it appears on the Bialive website for Healthcare Professionals, and we are sorry to hear that the anonymous felt the information provided was not sufficient. We aim to address their concerns over the next paragraphs.

A) Background Information on opicapone, contraindications and interactions with safinamide

Ongentys (opicapone) has been authorised in the European Union and UK since 2016, and is indicated as adjunctive therapy to preparations of levodopa/ DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations. Opicapone belongs to a class of anti-Parkinson's medications known as Catechol-O-Methyl Transferase Inhibitors (COMTi) which increase levodopa plasma levels by inhibiting a key enzyme responsible for its degradation, thereby improving the clinical response to levodopa.

The Summary of Product Characteristics for opicapone reports the following contraindications:

a) Hypersensitivity to the active substance or to any of the excipients.
b) Phaeochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.
c) History of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis.
d) Concomitant use with monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine and moclobemide) other than those for the treatment of PD

Please note the concomitant use of safinamide (a MAO-B inhibitor used in the treatment of PD) and opicapone is not contraindicated; in this regard, the Ongentys SPC also states (Section 4.5):

"There is no experience with opicapone when used concomitantly with the MAO-B inhibitor safinamide. Therefore, their concomitant use should be considered with appropriate caution"

The use of opicapone concomitantly with safinamide is therefore not contraindicated and represents a possible clinical decision if deemed appropriate by the prescribing clinician.

B) The OPTIPARK Study

OPTIPARK (BIAL-OPC-401) was a prospective open label, single-arm, multicentre trial studying the effectiveness of opicapone 50mg in Levodopa-treated patients with Parkinson's Disease (PD) experiencing motor fluctuations (MF). The aim of this study was to evaluate the change in patient's perception of their global conditions, assessed by the Clinician's Global Impression of Change Scale (CGI-C) after 3 months of routine clinical practice including once-daily opicapone. The study was sponsored by BIAL and carried out in 68 specialist neurology centres in Germany and the UK, and was registered at EudraCT (2016-002391-27) and clinicaltrials.gov (NCT02087442).

Enrolled patients included men and women aged ≥30 years, with idiopathic PD experiencing MFs and treated with Levodopa (LD) and DOPA-Decarboxylase Inhibitors (DDCIs). Patients were excluded if they presented with atypical parkinsonism, severe unpredictable OFF periods, and severe hepatic impairment; patients previously treated with tolcapone, opicapone or MAO-A and -B inhibitors other than those used for the treatment of PD (i.e. selegiline, rasagiline, or safinamide), were also excluded.

The primary outcome was the CGI-C (7-point scale, from "*very much improved*" to "*very much worse*"); secondary outcomes included the Patient's Global Impression of Change (PGI-C), Wearing-off Questionnaire (WOQ-9), Unified Parkinson's Disease Rating Scale (UPDRS) sections I-IV, Parkinson's Disease Questionnaire (PDQ-8), Non-motor Symptoms Scale (NMSS) and change from baseline in total daily LD dose and dosing frequency. Safety was assessed through reporting of treatment emergent adverse events (TEAEs) as well as vital signs and physical and neurological examinations.

506 patients were enrolled in the study, of which 495 constituted the Safety Set for further analyses; the majority of these patients (78.8%) were on another levodopa adjunct medication, including rasagiline (n=136, 27.5%), pramipexole (n=123, 24.8%), ropinirole (n=111, 22.4%), amantadine (n=105, 21.2%), rotigotine (n=68, 13.7%), safinamide (n=67, 13.5%), and piribedil (n=44, 8.9%).

When discussing the study results, the authors (Reichmann *et al.*) concluded that the results of this open-label study in PD patients with MFs confirmed the efficacy and safety profile of opicapone 50mg once daily as used in routine clinical practice. The majority of patients showed improvements in their perception about global PD condition (≥70% as judged by clinicians and patients themselves) 3 months after treatment initiation with opicapone 50mg once daily, and adverse events were in line with what was expected for a dopaminergic therapy in patients with PD.

This study mirrored a real-world clinical setting population and allowed the inclusion of a broader population of fluctuating PD patients than randomised controlled studies, although it was not designed to specifically study the safety of opicapone when used concomitantly with other anti-PD medications beyond Levodopa and COMTi's.

The efficacy and safety results of OPTIPARK were also submitted to Regulators such as the European Medicines Agency (EMA) at the point of the renewal of the Marketing Authorisation (MA) for Ongentys (Application R/0031, with opinion issued on 10/12/2020) as detailed in the European Public Assessment Report on page 7, stating:

"Since the date of Marketing Authorization in the EU, no new efficacy data originated from a phase III study was generated. However, a DB phase II study (ONO-2370-02) and an open label phase IV study (BIA-OPC-401) were concluded during this period. The phase II study demonstrated efficacy of OPC in the Japanese population, while the phase IV study provided real world data that reinforced the efficacy profile evidenced by the DB phase III studies. Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Ongentys in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity".

In the Renewal of Marketing Authorisation Assessment Report the European Medicines Agency positively appraised the results of OPTIPARK, adding that*: "The results of the different subgroup analyses showed that for the majority of subjects an improvement was reported regardless of age, disease duration at study entry and L-dopa mean daily dose, concomitant usage of COMT inhibitors, usage of COMT inhibitors before first IMP intake, concomitant usage of dopamine agonists, concomitant usage of monoamine oxidase inhibitors (MAO-Bi) and dopamine agonists at baseline"*.

Furthermore, when assessing the new clinical data (including OPTIPARK) presented at the point of MA renewal, the Agency concluded that: *"No new clinical data are available which change or result in a new benefit-risk balance evaluation. The product can be safely renewed at the end of this 5-year period for an unlimited period, and no action is recommended nor initiated. The authorities have been kept informed of any additional data significant for the assessment of the benefit-risk balance of the product. The product information is up to date with the current scientific knowledge including the conclusions of the assessments and recommendations made publicly available on the European Medicines web-portal".*

C) Allegation of discrepancy in the information provided in the Prescribing Information

The anonymous complainant has raised concerns that the current wording on the PI concerning the lack of clinical experience in the concomitant use of opicapone and safinamide is not accurate and could consequently lead to medication errors by omitting to inform Healthcare Professionals (HCPs) of the existence of a population of patients in a clinical trial where opicapone has been used in combination with safinamide.

In this regard, it is important to reflect that the statement quoted by the complainant in their letter *("There is no experience with opicapone when used concomitantly with the MAO-B inhibitor safinamide"*) is not fully reflective of the PI wording, which actually mirrors the SPC*: "There is no experience with opicapone when used concomitantly with the MAO-B inhibitor safinamide. Therefore, their concomitant use should be considered with appropriate caution"*.

Given the OPTIPARK study was carried out with the aim of studying the efficacy and safety of opicapone within its licensed indication in a real-world clinical practice population and was not intended to study in detail the feasibility of combining opicapone with other PD medications beyond LD and COMTis, we believe the current wording is factually correct and reflects the efficacy and safety profile of the product as appraised by Regulatory Authorities to date. Given the SPC is a regulatory document, and its wording may only change following a decision by the relevant Authority, we feel that any deviation in the PI wording with regards to the concomitant use of opicapone and safinamide may lead readers to overestimate the magnitude of data currently existing and not allow them to form a full opinion of the therapeutic value of opicapone.

We believe we have acted in line with the spirit of the Code and not advocated a course of actions which would have resulted in breaches of the Code, therefore clauses 6.1 and 5.1 have not been breached. We also consider that we have not acted in such a way to prejudice patients' safety and reduce confidence in the Pharmaceutical Industry, and consequently we have not breached clause 2.

D) Clarity of Prescribing Information on the Internet

The anonymous complainant accessed the copy of the Prescribing Information on the HCPs section of the Bialive website to validate the information on the concomitant use of opicapone and safinamide. The complainant has found the navigation challenging

for the presence of multiple identification codes and disclaimers on the website and has provided the PMCPA with a pdf printout of the web page.

The PI page on the Bialive website is designed to provide HCPs with an easy-to-access electronic copy of the Prescribing Information and is made of different sections, which are certified separately:

1. UK/ON/2024/001(1)
Ongentys (opicapone) Prescribing Information – Date of Preparation: January 2024
Certified on: 19th January 2024 by [named medical signatory]

2. UK/ON/2024/002(2)
Ongentys (opicapone) PI page on Bialive – Date of Preparation: January 2024
Certified on: 19th January 2024 by [named medical signatory]

3. UK/ON/2023/064(1)
Bialive HCP Footer – Date of Preparation: January 2024
Certified on: 22nd January 2024 by [named medical signatory]

The full web page therefore bears three job bag codes and dates of preparation (one for each of the sections certified separately) as well as the obligatory AE reporting information and a disclaimer at the top of the screen advising the visitor that the information provided is intended for UK and Irish HCPs only.

While we appreciate the reader may have found the presence of many identification codes distractive, we have added this information to fulfil our obligations under the Code, and to facilitate the internal process of selectively update each section as and when needed. Furthermore, the size and positioning of the identification codes have been chosen to emphasize the main content of the page (i.e. the Prescribing Information and Adverse Events Reporting Statement) while keeping the codes and disclaimers visible.

We also note that the screenshot provided by the complainant did not represent the actual appearance of the web page and was probably obtained by selecting the “Print as pdf” option on the web browser without choosing to include the Background Graphics in the output. Consequently some background graphics are missing, some of the disclaimers appear as they have been shrunk, and the page does not appear in its actual format. When we have tried to replicate the same screenshot and include the Background Graphics, the problem has not occurred and the legibility of the web page appeared satisfactory.

We consider this web page has been designed and certified to be legible and unambiguous, therefore we have acted in line with the requirements of the Code and maintained high standards. Consequently, we have not breached Clause 6.1 (the material was sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine), nor Clause 5.1 (we have maintained high standards) or Clause 2.

I trust the information provided in this letter has been helpful to clarify the allegation regarding our Prescribing Information and reiterated our commitment to operate in line with the expected high standards required by the Code."

PANEL RULING

This case was in relation to the prescribing information for Ongentys (opicapone) in which the complainant alleged there was a discrepancy with respect to the concomitant use of Ongentys with the MAO-B inhibitor safinamide.

The complainant alleged that a Bial representative had communicated that Ongentys could be safely administered concomitantly with levodopa, carbidopa and safinamide in a patient experiencing motor fluctuations, but the Ongentys prescribing information allegedly stated, *"there is no experience with opicapone when used concomitantly with the MAO-B inhibitor safinamide".* The complainant was aware of the OPTIPARK study in which 67 patients took opicapone and safinamide together, and was concerned that this discrepancy in the prescribing information was a significant issue and could lead to incorrect medical practices.

The complainant had confirmed that their complaint was specifically related to the accuracy of the prescribing information and had no concerns regarding the interaction with the representative.

The complainant made a further allegation with respect to the navigation and clarity of the prescribing information due to "*multiple identification codes and repetitive disclaimers*".

The Panel considered the allegations regarding the content of the prescribing information and the navigation of the prescribing information separately.

Content of Prescribing Information

As outlined above, the complainant alleged there was a discrepancy in the Ongentys prescribing information regarding concomitant use with safinamide, given the differing information provided to them by a representative and their awareness of a study which included patients using these products together.

Bial submitted that the prescribing information wording regarding safinamide mirrored the information in the Summary of Product Characteristics (SPC) for Ongentys. It further submitted that the OPTIPARK study referenced by the complainant was a prospective open label, single-arm multicentre trial which studied the efficacy and safety of opicapone within its licensed indication in a real-world clinical practice population and was not designed to study in detail the safety of concomitant use of opicapone with other Parkinson's Disease treatment beyond levodopa and COMTis (Catechol-O-Methyl Transferase Inhibitors). Furthermore, Bial submitted that given that the SPC was a regulatory document in which the wording could only be changed following a decision from the relevant regulatory authority, a deviation in the prescribing information may lead readers to overestimate the magnitude of data currently existing.

The Panel noted that the complainant had provided both a link to the webpage containing the Ongentys prescribing information on the 'Bialive' website and a pdf version of what appeared to be the same prescribing information.

The prescribing information, in a section headed 'Contraindications' stated, among other things, *"Concomitant use with monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine and moclobemide) other than those for the treatment of Parkinson's disease"*.

Further to this, the prescribing information, in a section headed 'Drug interactions' stated, among other things, *"There is no experience with opicapone when used concomitantly with the MAO-B inhibitor safinamide. Therefore, their concomitant use should be considered with appropriate caution"*.

Clause 6.1 states: *"Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis".*

Clause 12.2 requires that the prescribing information consists of specific information including: *"a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics,…"* (emphasis added by the Panel).

Whilst information about drug interactions was not listed as a specific requirement of prescribing information, the Panel considered that any information included in the prescribing information should be accurate and reflect the information within the SPC.

The SPC for Ongentys, section 4.2 Contraindications, included: "*Concomitant use with monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine and moclobemide) other than those for the treatment of Parkinson's disease (see section 4.5)*".

Section 4.5 of the SPC, 'Interaction with other medicinal products and other forms of interaction' stated: *"There is no experience with opicapone when used concomitantly with the MAO-B inhibitor safinamide. Therefore, their concomitant use should be considered with appropriate caution"*.

The Panel accepted Bial's submission that the concomitant use of safinamide (a MAO-B inhibitor used in the treatment of Parkinson's Disease) and opicapone is not contraindicated. In the Panel's view, the information regarding concomitant use with safinamide in the Ongentys prescribing information was not inconsistent with the SPC.

The Panel accepted Bial's submission that the OPTIPARK study was not designed to study in detail the feasibility of combining opicapone with safinamide. The Panel considered Bial's submission that any deviation in the prescribing information wording with regard to the concomitant use of opicapone and safinamide may lead readers to overestimate the magnitude of data currently existing and not allow them to form a full opinion of the therapeutic value of opicapone.

Taking the above into consideration, the Panel concluded that the prescribing information was not inaccurate or misleading in relation to the concomitant use of opicapone with safinamide and **ruled no breach of Clause 6.1**. The complainant had not established that Bial had failed to maintain high standards in this regard or prejudiced patient safety. The Panel therefore ruled **no breaches of Clauses 5.1 and 2**.

Navigation of Prescribing Information

The complainant alleged that the prescribing information webpage was difficult to navigate due to "*multiple identification codes and repetitive disclaimers*".

The Panel noted that the complainant had provided both a link to the webpage containing the Ongentys prescribing information on the 'Bialive' website and a pdf version of what appeared to be the same webpage. The pdf version appeared different to what was visible when accessing the link, with some sections appearing blurred, possibly due to the complainant printing the webpage to pdf when obtaining a pdf version. The screenshot of the webpage accessed via the link, taken by the case preparation manager at the time of the complaint, matched the version that was provided by Bial as part of its submission. Therefore, the Panel based its ruling on this version.

The Panel observed that the webpage contained three job codes which appeared in the following locations: one at the end of the prescribing information, one at the end of the webpage (above the footer) and one within the footer. The Panel noted that the first job code appeared immediately underneath the prescribing information, adjacent to the date of preparation. The second and third job codes were in a small font, visibly smaller than the text of the prescribing information, and none of the three job codes overlaid the text of the prescribing information.

Bial submitted that the webpage included three different job codes, corresponding to three different job bags which had been certified – Ongentys Prescribing Information, the Ongentys prescribing information webpage on Bialive and the Bialive health professional website footer. The job codes were included to fulfil its obligations under the Code and to facilitate its internal process for selectively updating each section as required. Bial submitted that the size and positioning of the job codes had been chosen to emphasise the main content of the webpage – the prescribing information and adverse event reporting statement, while keeping the job codes and disclaimers visible.

The Panel noted that no specific clause relating to prescribing information had been raised by the case preparation manager and so considered this matter under Clause 5.1.

The Panel noted that the Code did not refer to 'job codes' but they were referred to in the Guidelines on Company Procedures Relating to the Code of Practice for the Pharmaceutical Industry in relation to 'Certification and Examination'. It was advised that for materials that are required to be certified under the Code, each certificate should bear a reference number with the same reference number appearing on the material, item, etc. in question or some other means so that there can be no doubt as to what has been certified and the certificate can be matched to the material. Therefore, it appeared to the Panel that the job codes were included on the separately certified components of the webpage, in accordance with the guidelines.

The Panel was unclear what the complainant was referring to by "*repetitive disclaimers*". A disclaimer was observed at the very top of the webpage which stated: *"This site is intended for healthcare professionals in the UK and Republic of Ireland only. If you would like to visit the public area please visit [URL provided]"*. The disclaimer appeared in a separate dark blue banner to the white background of the prescribing information. In addition, an adverse event reporting statement appeared twice on the webpage, once beneath the prescribing information but in a separate blue box and again in the footer within a separate box. There also appeared to

be a 'cookie' disclaimer which was visible on the first half of the webpage in the screenshot taken by the case preparation manager.

A prominent adverse event reporting statement was a Code requirement for all promotional material, as stated in Clause 12.9. In addition, supplementary information to Clause 16.1 stated: *"unless access to promotional material about prescription only medicines is limited to health professionals and other relevant decision makers, a pharmaceutical company website or a company sponsored website must provide information for the public as well as promotion to health professionals with the sections for each target audience clearly separated and the intended audience identified."* (emphasis added by the Panel). Therefore, it appeared to the Panel that the disclaimers present on the prescribing information webpage were necessary to fulfil these specific Code requirements. The Panel noted that none of the above disclaimer text overlaid the content of the prescribing information.

In considering whether the prescribing information webpage was challenging or difficult to navigate due to multiple identification codes and repetitive disclaimers, the Panel took account of the following:

1. Job codes appeared in a small font, visibly smaller than that of the prescribing information. They did not appear to be obtrusive to the Panel nor distract from the content of the prescribing information.
2. Although not a Code requirement, PMCPA guidance advises that for certified material, each certificate should bear a reference number with the same reference number appearing on the material.
3. The disclaimers appearing on the webpage were necessary to fulfil Code requirements and did not interfere with the content of the prescribing information.

Taking the above into consideration, the Panel concluded that the complainant had not established that the prescribing information webpage was challenging or difficult to navigate due to multiple identification codes and repetitive disclaimers, and ruled **no breach of Clause 5.1** in this regard.

* * * * *

During its consideration of this case, the Panel was concerned to note that it appeared that the sales representative had verbally provided information to the complainant which was inconsistent with the Ongentys SPC with regard to concomitant use with safinamide. Representatives must maintain a high standard of ethical conduct in the discharge of their duties and comply with all relevant requirements of the Code, including that the promotion of a medicine must not be inconsistent with the particulars listed in its SPC. The Panel requested that Bial be advised of its concerns in this regard.

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Complaint received **5 August 2024**

Case completed **9 September 2025**