CASE/0221/07/24 ***NO BREACH OF THE CODE***

COMPLAINANT v GSK

Allegations about a Zejula (niraparib) safety webpage

CASE SUMMARY

This case was in relation to a safety claim which appeared on a GSK promotional website aimed at UK healthcare professionals. The complainant alleged that the claim, which appeared on the safety overview webpage and included the wording "manageable safety profile", was incorrect, misleading and unqualified.

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	**Requirement to maintain high standards at all times**
No Breach of Clause 6.1	**Requirement that information must be accurate, up-to-date and not misleading**
No Breach of Clause 6.2	**Requirement that information/ claims/ comparisons must be capable of substantiation**

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 about GSK was received from an anonymous, contactable complainant, who later became non-contactable, and described themselves as a health professional.

COMPLAINT

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

> "GSK had a number of breaches across a range of areas regularly over the last few years. Therefore, it was shocking that safety claims for Zejula were not in line with the spirit and letter of the Code. [URL] May 2024 | PM-GB-NRP-WCNT-220021 On the Zejula safety overview promotional page, a headline claim was made: ZEJULA (niraparib) 1L monotherapy as a maintenance treatment demonstrated a manageable safety profile in two phase III clinical trials, PRIMA and PRIME. This was incorrect as adverse events in both trials led to discontinuation of Zejula treatment. In Prima 13.8% of patients discontinued therapy due to side effects. In Prime 6.7% of patients discontinued

therapy due to adverse events. Considering the % of discontinuation due to side effects in both trials, the headline claim on the page that Zejula has a manageable safety profile is a major risk to patient safety and is misleading to a significant degree considering the claim had not been qualified by the rates of discontinuation directly as a result of side effects in both trials. [Information separate to the complaint]. Repeat breaches of the Code was not in line with self-regulation objectives. 6.1 + 6.2 + 5.1 + 2 had been breached."

When writing to GSK, the PMCPA asked it to consider the requirements of Clauses 6.1, 6.2, 5.1 and 2 of the 2021 Code.

GSK'S RESPONSE

The response from GSK is reproduced below:

"GSK was extremely disappointed to have received a letter dated 4th July 2024 from the PMCPA informing us of a complaint from an anonymous individual describing themselves as a healthcare professional regarding the above. The PMCPA asked GSK to bear in mind the requirements of Clauses 6.1, 6.2, 5.1 and 2 of the 2021 Code, as cited by the complainant.

The complainant alleged that "*it was shocking that safety claims for Zejula were not in line with the spirit and letter of the code (sic)*". Specifically, the complainant considered that the claim, "*ZEJULA (niraparib) 1L monotherapy as maintenance treatment demonstrated a manageable safety profile in two phase III clinical trials PRIMA and PRIME" was "incorrect as adverse events in both trials led to discontinuation of Zejula treatment*". The complainant cited promotional webpage PM-GB-NRP-WCNT-220021 (v2.0), containing the claim which they stated breached Clauses 6.1, 6.2, 5.1 and 2 of the Code.

GSK takes its responsibility of abiding by the letter and the spirit of the Code and all other relevant UK rules and regulations very seriously. Following the complaint, we temporarily took down all relevant webpages while we reviewed the material in question, as well as to review our internal ways of working and processes. Following our review, GSK is comfortable that both our processes and the materials in question are of suitable quality and of a high standard and are therefore in line with the Code as they are. Consequently, we deny breaches of Clauses 6.1, 6.2, 5.1 and 2 of the Code.

GSK has laid out the specific responses to the individual clauses the PMCPA has asked us to consider in detail below.

Website background

The ZEJULA (niraparib) webpage referred to in the complaint is part of a more extensive promotional website called GSKPro, which is aimed at UK Healthcare Professionals (HCPs). The website contains promotional information about all GSK medicinal products currently marketed in the UK. Within the website there is a section dedicated entirely to the product ZEJULA. The complainant's allegations relate to only some of the pages from this section but not all.

The ZEJULA website can be accessed by two methods:

- Direct access by HCPs via a search engine, such as Google, that requires confirmation that they are an HCP via a pop up, as opposed to a member of public for whom there is a link to a separate part of the website with relevant content.
- Via promotional materials including GSK generated emails and 3rd party banner adverts linking directly to the website.

GSK processes and structure

GSK has robust processes and structures for material approval to ensure compliance with the Code, GSK's own code, and UK regulations. All employees involved in copy approval must complete mandatory GSK copy approval SOP training. Each brand team holds a regular forum for discussion and agreement (FDA), involving medical and commercial teams, to discuss materials requiring copy approval, to align fully and ensure Code-compliant content. Where views differ, such as those over specific claims, there is a clear and well-established route of escalation for resolution.

To maintain ongoing Code knowledge, GSK conducts a monthly Code Forum meeting in which Code cases are presented and discussed as well as any other compliance/ governance issues which merit awareness. While the meeting is intended principally for all medical signatories, commercial reviewers and content owners, other staff interested to attend for their own learning and development may do so. Attendance is consistently strong, and materials discussed are stored on GSK's internal governance platform, accessible to all UK employees.

Additionally, GSK holds Governance meetings once a month for medical signatories and medical reviewers. Attendees raise Code-related agenda items for discussion, with a view to reaching consensus within the group, under the guidance of experienced senior signatories.

Furthermore, GSK has a fair and objective process for assessing and validating not only medical signatories, but also commercial reviewers. The role of the commercial reviewer is to provide commercial overview of all promotional and relevant non-promotional materials for appropriateness, including fundamental aspects and principles of the Code, as well as content suitability and strategic alignment. These assessments involve one, or more often two assessors, objectively questioning the candidate on case examples, covering multiple aspects of the Code. In addition, the appraisee must have completed a set of mandatory training requirements. In the case of medical signatories, the appraisee must have been mentored for a period by another experienced medical signatory, until the mentor deems the appraisee ready to take the assessment to become a final medical signatory.

[information separate to the complaint]

ZEJULA and disease background

ZEJULA is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1, and PARP-2. These enzymes play a key role in DNA damage repair. In vitro studies have

shown that ZEJULA-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes. These effects result in DNA damage, apoptosis, and cell death within the tumour. Increased niraparib-induced cytotoxicity was observed in tumour cell lines with or without deficiencies in the BReast CAncer (BRCA) 1 and 2 tumour suppressor genes. ZEJULA has two licensed indications which are:

- as monotherapy for the maintenance treatment of adult patients with advanced epithelial (International Federation of Gynaecology and Obstetrics, FIGO, Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer. ZEJULA is prescribed by specialist oncologists to such patients who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. ZEJULA is prescribed by specialist oncologists to such patients who are in response (complete or partial) to platinum-based chemotherapy.

ZEJULA was granted an EU Marketing Authorisation for the relapsed indication in November 2017 and the first line indication in November 2020. It was licensed by the European Medicines Agency in the first line setting based on the pivotal phase 3 results of PRIMA. PRIMA was a registrational Phase 3 double-blind, placebo-controlled trial in which patients (n = 733) in complete or partial response to first-line platinum-based chemotherapy for gynaecological cancers were randomised 2:1 to ZEJULA or to matched placebo. ZEJULA demonstrated a favourable benefit/risk profile resulting in its marketing authorisation in the first line setting for the specific patient sub-group with ovarian cancer described above.

PRIME was a Phase 3 double-blind, placebo-controlled trial in which patients (n = 384) in complete or partial response to first-line platinum-based chemotherapy were randomised 2:1 to ZEJULA or matched placebo which took place in China. The key differences between the PRIME and PRIMA trials are:

- PRIME included patients irrespective of postoperative residual disease (RD) status, including R0 (no residual tumour) after primary cytoreductive surgery. Inoperability was an exclusion criterion in PRIME.
- PRIME prospectively applied individualised starting doses. The standard starting dose of niraparib was 200 mg, taken once daily. However, for those patients who weighed ≥77 kg and had baseline platelet counts ≥150,000/µL, the starting dose was 300 mg once daily. These are also the licensed starting doses as per the SmPC in the UK.
- PRIME used the homologous recombination deficiency (HRD) assay from BGI Genomics, which had not been validated in prior clinical trials and was not known to be interchangeable with the Myriad myChoice® CDx HRD test used in the PRIMA trial.
- In PRIME, stratification factors included germline breast cancer gene mutation (gBRCAm) status (gBRCAm/non-gBRCAm), tumour HRD status (homologous

recombination deficient [HRd]/HRp or homologous recombination status not determined [HRnd], neoadjuvant chemotherapy (NACT) and response to 1L platinum-based chemotherapy (CR/PR).

Clause 6.1

The complainant alleges with respect to the item PM-GB-NRP-WCNT-220021, dated May 2024 on the GSKPro website, "it *was shocking that safety claims for Zejula were not in line with the spirit and letter of the code (sic)".* Specifically, the complainant cited the claim on the Safety Overview page, *"ZEJULA (niraparib) 1L monotherapy as a maintenance treatment demonstrated a manageable safety profile in two phase III clinical trials, PRIMA and PRIME".*

With respect to the Code, GSK holds itself to the highest standards possible and disagrees strongly with the complainant's incorrect assertion that the safety claims for ZEJULA were not in line with the spirit and letter of the Code. GSK remains confident that the overall information provided on the webpage, and indeed on the entire ZEJULA promotional website, is balanced, fair, objective, and unambiguous. The information is based on the most up-to-date evidence and that evidence is reflected accurately and clearly. The information does not mislead either directly or by implication, distortion, exaggeration, or undue emphasis.

The approved SmPC for ZEJULA contains the most up-to- date and robust information on the product. All SmPC product information, including the safety information challenged by the complainant, has been reviewed by and agreed with the relevant, competent Regulatory Authorities. Section 4.2 of the ZEJULA SmPC, details the dose modifications recommended to be made for adverse reactions. The SmPC clearly states there that: "In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to interrupt the treatment and then resume at the lower dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended that ZEJULA be discontinued. **If adverse reactions are not manageable with this strategy of dose interruption and reduction, it is recommended that ZEJULA be discontinued**." (GSK-added bold emphasis). This key guidance provides healthcare professionals with a summary of the recommended safety management strategy. It clearly incorporates discontinuation of ZEJULA as an integral part of patients' clinical oversight and care. Specific details for managing adverse events (AEs) with ZEJULA are detailed in tables 1, 2 and 3 of the SmPC. These tables all incorporate discontinuation as part of patient management. Specific information is also available in the GSKPro safety section including how to monitor patients as well as the overarching management, detailed in Table 1 from the SmPC, with clear signposting to the SmPC for full details.

For the above reasons, GSK disagrees strongly with the complainant's allegation, "*Considering the % of discontinuation due to side effects in both trials, the headline claim on the page that ZEJULA has a manageable safety profile is a major risk to patient safety and is misleading to a significant degree considering the claim has not been qualified by the rates of discontinuation directly as a result of side effects in both trials*". GSK and relevant prescribing specialist HCPs are fully aware that the standard clinical management of AEs, especially in oncology, invariably includes dose reduction,

omission of dosage and/or discontinuation of medication. Thus, discontinuation of medication as part of a management strategy is fundamental and a well-established practice not only in clinical oncology but in all other therapy areas. This AE management guidance was available consistently to UK healthcare professionals viewing the website. It was provided in full via the clear hyperlink to the ZEJULA SmPC. The management of adverse events for ZEJULA was further reinforced via a second mechanism within the safety profile section on the website. That section included monitoring requirement details for ZEJULA and specifically included Table 1 from the SmPC. As already advised, Table 1 details recommended dose modifications for adverse reactions, including when discontinuation as part of standard management for adverse events is appropriate.

PM-GB-NRP-WCNT-220021 addresses the safety data available for ZEJULA in the first line advanced ovarian cancer setting. GSK is of the view that while the claim in question validly stands alone, it is accompanied by clear signposting to the additional, detailed safety data for both PRIMA and PRIME clinical studies. The detailed data section provides HCPs with a full overview of the adverse events reported in each of the two phase III ZEJULA clinical trials. The dedicated ZEJULA Safety Section is accessible from a drop-down menu. When selected, healthcare professionals have access to clear information on ZEJULA monitoring including adverse event management, as well as access to full details of the safety and tolerability profile for ZEJULA. This approach to detailing product safety information, illustrates GSK's commitment to facilitate specialist gynae-oncologists' access to comprehensive safety (as well as efficacy) data, thereby supporting the informed, rational use of an important medicinal product licensed for the specialist management of serious gynaecological malignancies.

GSK further notes that the inclusion of treatment discontinuation as an integral part of safety management is, unsurprisingly, not unique to ZEJULA. This approach is standard practice with other PARPi products used in oncology. Discontinuation is similarly clearly documented in the SmPCs for medicines in the same therapeutic class. That the risk-benefit profiles of PARPi's are considered as generally manageable is recognised and documented within the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines. Specialist Oncologists prescribing such therapeutic agents are familiar with the ESMO Guidelines.

To provide additional context, the table below summarises discontinuation rates following adverse events in trials for similarly relevant medications prescribed in the NHS:

	Advance Ovarian cancer 1L PARPi trials	Licensed medication	Medication discontinuation rate due to any AE
Moore 2018	SOLO-1	Olaparib	12% (30 patients)
Monk 2022	ATHENA-MONO	Rucaparib	11.8% (50 patients)
Gonzalez 2022	PRIMA	Niraparib	13.8% (67 patients)

As stated in the SmPC, "Treatment with ZEJULA should be initiated and supervised by a physician experienced in the use of anticancer medicinal products." Such specialists

have considerable experience managing the safety profile of important anticancer medicines including ZEJULA.

It is also relevant to consider and acknowledge the nature of underlying diseases requiring oncological treatments where the risk-benefit ratio may, of necessity differ from other less aggressive medical conditions. This has already been acknowledged by the PMCPA in a previous Code case of an anonymous oncologist v Pierre Fabre (AUTH/2799/10/15). In that ruling, the Panel: '...noted the highly specialised therapy area … In the Panel's view the audience would be familiar with the side effect profile of cytotoxic medicines generally.' Oncology treatments that are life prolonging and/or reduce disease relapses can be associated with severe adverse reactions that may be unavoidable. Consequently, what is deemed manageable and tolerable within the oncology community may differ from clinical perspectives in other specialty areas.

GSK also contends that while the claim in question stands alone, clear, prominent links to the SmPC and the PRIMA and PRIME data direct HCPs to other areas of GSKPro dedicated to detailed ZEJULA safety information. These links have been positioned immediately below the claim and demonstrate that every reasonable opportunity was taken to represent all safety information comprehensively and correctly. This approach is a clear contradiction of the complainant's claim that incorrect and misleading information was provided by GSK.

In summary, GSK disagrees strongly with the complainant's assertion that, "i*t was shocking that safety claims for ZEJULA were not in line with the spirit and the letter of the code (sic)*". Specialist Oncology HCPs are required routinely to respond to adverse events and/ or drug-related unwanted side-effects. As detailed above, managing complex therapeutic decisions encompasses a spectrum of possible actions balancing the effectiveness of a treatment with the severity of any side effects that may arise. An appropriate and routinely employed management option is to discontinue some or all of a treatment regimen. Stating that ZEJULA has a 'manageable safety profile' is wholly consistent with such an approach. GSK strongly refutes the complainant's allegation that the referenced headline is "*a major risk to patient safety and is misleading to a significant degree*". The information presented by GSK for ZEJULA in its promotional materials is entirely consistent with the product's marketing authorisation, its SmPC and clinical consensus from relevant, experienced Healthcare Professionals who prescribe ZEJULA and manage patients' therapeutic responses accordingly.

Consequently, GSK maintains that the claim is accurate, balanced, fair, and reflects current evidence on ZEJULA's safety profile. Discontinuation, when indicated, for the management of adverse events is standard clinical practice and entirely consistent with the SmPC for ZEJULA. For these reasons, we disagree that the Company is in breach of Clause 6.1.

Clause 6.2

The complainant also alleged a breach of Clause 6.2 indicating their belief that the claim "ZEJULA (niraparib) 1L monotherapy as a maintenance treatment demonstrated a manageable safety profile in two phase III clinical trials, PRIMA and PRIME" is not capable of substantiation." Three references substantiating the claim are included clearly on the website. The first reference is for the PRIMA primary analysis, and the second is

for the PRIMA 3.5-year patient follow up; both references discuss the safety profile of ZEJULA in detail and include the number of modifications, interruptions and discontinuations to treatment due to adverse events. It is both noteworthy and relevant that the study protocol followed the same approach to AE management documented in Table 1 of the ZEJULA SmPC. The third reference, to the PRIME trial confirms, once again, that the study protocol required the same approach to AE management that has been incorporated as Table 1 in the ZEJULA SmPC. The PRIME publication (Li et al) states the discontinuation rates and modifications to the drug regimen needed. HCPs are referred to the supplementary information for further comprehensive detail on the safety profile for ZEJULA.

Consequently, GSK provided full substantiation for the ZEJULA safety claims proactively in its material by including the relevant supporting publications and the SmPC for ZEJULA. We note that the complainant referred to Clause 6.2 in general terms regarding this claim. Although Clause 6.2 also states that companies must provide substantiation following a request for it, GSK has not received any such requests prior to receiving this complaint.

Therefore, based on the above, GSK strongly denies any breach of Clause 6.2.

Clause 5.1

As discussed earlier, GSK processes, training, governance, and management monitoring have all been designed and implemented to embed the spirit as well as the letter of the Code. GSK's standards promote rigour when creating, reviewing, approving, and certifying promotional materials. We remain confident that the certification process and the quality of the cited materials are robust. All claims and content including the safety claims raised by the complainant, were critically appraised, deemed correct and suitable, thereby meeting the high standards required by the Code.

Consequently, GSK strongly believes that high standards were maintained and there has not been a breach of Clause 5.1.

Clause 2

The PMCPA also asked GSK to bear in mind the requirements of Clause 2 of the Code. GSK notes that a ruling of a breach of Clause 2 is a sign of censure, reserved for circumstances that include prejudicing patient safety and/or public health. It is ruled when significant failings have been identified, that include *inter alia* a risk to patient safety.

In responding to the breaches alleged by the complainant, GSK has argued cogently that there is no evidence of a risk to patient safety, or a failure in the Company's systems and processes. The webpage in question was reviewed, certified and the final form examined in the manner required and to the standards mandated by the Code and by GSK's own SOP. Furthermore, GSK has demonstrated that the claim at issue is fully supported and is substantiated by the clinical evidence described above. GSK takes patient safety very seriously. We believe strongly that patient safety has not been nor will be prejudiced by the materials and claim in question.

For these reasons, and all others detailed above, GSK's activities and materials do not risk bringing discredit upon or reducing confidence in the pharmaceutical industry. Consequently, GSK does not recognise that there has been a possible breach of Clause 2.

[Information separate to the complaint]

Additional information

The signatory who reviewed, approved, and certified the material at issue in Case/0221/07/24 is a registered UK pharmacist with [X] years' signatory experience and over [Y] years' experience in the pharmaceutical industry. The signatory has been a registered pharmacist since [date] and was previously a pharmacist providing NHS services.

Summary

GSK takes its responsibility of abiding by the letter and the spirit of the Code extremely seriously. As laid out in our detailed response above, GSK denies breaches of Clauses 6.1, 6.2, 5.1 and 2 of the 2021 ABPI Code of Practice."

PANEL RULING

This case related to a safety claim which appeared on a section dedicated to Zejula (niraparib) on a GSK promotional website aimed at UK healthcare professionals. The complainant alleged that the claim "ZEJULA (niraparib) 1L monotherapy as a maintenance treatment demonstrated a manageable safety profile in two phase III clinical trials, PRIMA and PRIME" was misleading and unqualified.

Zejula was an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2 and had two licensed indications, as monotherapy for the maintenance treatment of adult patients with:

1. advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy, and

2. platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The Panel considered the layout and the overall impression created by the webpage containing the claim at issue, which was intended for health professionals.

The claim appeared on the "Overview" page under the "Safety Profile" tab. The claim appeared under the prominent heading "Safety Overview" and was followed by a text box with the wording "For a full list of Adverse Events and Special Warnings and Precautions please click here to view the Summary Product of Characteristics (SPC) for ZEJULA". Two subsequent, prominent blue boxes, one for the PRIMA safety profile and one for the PRIME safety profile, each had a

"LEARN MORE" button which took the reader through to more detailed safety information for the clinical studies. Beneath this was a box cautioning direct comparison between the two trials and a 'Find out more' section with links to 'study design' and 'efficacy' for both trials. Further information included the Zejula indication along with abbreviations, references and adverse event reporting statement. In the header, overview pages for both trials, their safety profiles, reported treatment emergent adverse events (TEAEs) and monitoring and adverse event management all appeared under the Safety Profile tab as part of a drop-down menu.

The Panel noted the complainant's overarching concern that the claim that Zejula had a "manageable safety profile" was incorrect and not appropriately qualified, despite the discontinuation rates reported in each trial due to adverse events: 13.8% in PRIMA and 6.7% in PRIME.

Section 4.2 of the SPC (Posology and method of administration)

The Panel considered Section 4.2 of the SPC (Posology and method of administration), which stated that treatment with Zejula "should be initiated and supervised by a physician experienced in the use of anticancer medicinal products". Under the sub-heading "Dose adjustments for adverse reactions", it provided further detail about managing TEAEs through interruption, dose modification and discontinuation as outlined in three tables. The recommended dose modifications for adverse reactions were listed in Tables 1, 2 and 3. Before the three tables, there was an introductory paragraph:

> "In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to interrupt the treatment and then resume at the lower dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended that Zejula be discontinued. If adverse reactions are not manageable with this strategy of dose interruption and reduction, it is recommended that Zejula be discontinued."

Table 1 ("Recommended dose modifications for adverse reactions"), outlined that patients starting at 200 mg/day could reduce to 100 mg/day before discontinuation, whereas those starting at 300 mg/day could reduce in two steps: first to 200 mg/day, then to 100 mg/day, with further reduction requiring discontinuation.

Table 2 ("Dose modifications for non-haematologic adverse reactions") recommended withholding treatment for a maximum of 28 days and resuming at a reduced dose, for non-haematologic TEAEs of CTCAE [common terminology criteria for adverse events] Grade ≥3 where prophylaxis was not feasible or the reaction persisted despite treatment. Upon recurrence, treatment should again be withheld and either resumed at a lower dose or discontinued. Where Grade 3 or above adverse events persisted beyond 28 days at the lowest permitted dose (100 mg/day), treatment discontinuation was the recommendation.

Table 3 ("Dose modifications for haematologic adverse reactions") highlighted the need for close monitoring of complete blood counts, particularly during the first month of treatment. For example, in the case of platelet counts below 100,000/μL, treatment should be withheld and resumed at the same or reduced dose if levels recovered. However, if platelet counts did not return to acceptable levels within 28 days, or the patient had already been reduced to 100 mg/day, Zejula should be discontinued. Similar guidance applied to neutrophil counts <1,000/μL

or haemoglobin <8 g/dL, and in the event of a confirmed diagnosis of myelodysplastic syndrome or acute myeloid leukaemia, treatment was to be permanently discontinued.

The Panel observed that discontinuation of treatment was provided in the table as the only option for a confirmed diagnosis of myelodysplastic syndrome or acute myeloid leukaemia and where Grade 3 and above non-haematologic adverse reactions occurred for longer than 28 days at 100mg/day. In all other listed adverse reactions discontinuation appeared as a final option following withholding, resuming and/or reduced dosing.

GSK submissions

The Panel noted GSK's submission that the inclusion of treatment discontinuation was not unique to Zejula, it was standard practice with PARPi products used in oncology. GSK referred to the 2023 ESMO Clinical Practice Guidelines (Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up) which recommended the use of niraparib for maintenance therapy of patients with high-grade tubo-ovarian carcinoma and described the toxicity of PARPis as "generally manageable through dose individualisation (for niraparib), dose reductions and dose interruptions".

GSK further provided discontinuation rates from clinical trials of comparable medicines, including 12% for olaparib and 11.8% for rucaparib, which the Panel noted were due to adverse reactions similar to those leading to discontinuation with niraparib (13.8%).

GSK submitted that while the claim in question stood alone, clear, prominent links to the SPC, PRIMA and PRIME data directed readers to other areas of the website dedicated to detailed Zejula safety information. In this regard, the Panel observed the claim at issue preceded prominent blue PRIME and PRIMA safety profile boxes which, when clicked, directed visitors to safety webpages for each trial.

The PRIMA trial

On the PRIMA page, the claim "In PRIMA, Zejula (niraparib) had a manageable safety profile, maintained over 3.5 years of median follow-up" appeared under the prominent title "PRIMA Safety profile". Further down the page, a table presented data on the incidence of treatment-emergent adverse events and included a 72.9% incidence of Grade ≥3 TEAEs in the treatment group compared to 23% in the placebo group. The table also included rates (niraparib vs placebo) of:

- treatment discontinuation (13.8% vs 2.9%),
- dose reduction (71.7% vs 9.4%),
- dose interruption (80.4% vs 20.9%), and
- treatment-related deaths (1.0% vs 0.8%).

Beneath the table, in bold text, the 13.8% discontinuation rate was reiterated alongside a 2.9% comparative figure for placebo, and a boxed cautionary statement:

> "ZEJULA should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with anti-hypertensive therapy. For suspected MDS/AML or prolonged haematological toxicities, the patient should be referred to a haematologist for further evaluation. If MDS/AML is confirmed ZEJULA,

treatment should be discontinued and the patient treated appropriately. In case of PRES, it is recommended to discontinue ZEJULA and to treat specific symptoms including hypertension. Please refer to full SmPC for further information."

The Panel noted the primary PRIMA trial analysis had a median duration of follow-up of 13.8 months (Gonzalez et al., 2019). The results presented on the GSK webpage were from its updated ad hoc analysis after a median 3.5 year follow up (Gonzalez et al., 2023). In the overall population, the most common grade ≥ 3 TEAEs in the niraparib arm were thrombocytopenia (39.7% vs 0.4%), anaemia (31.6% vs 2%), and neutropenia (21.3% vs 1.6%). Myelodysplastic syndromes or acute myeloid leukaemia events were reported in the same proportion of patients in the treatment and placebo arms.

The PRIME trial

On the PRIME page, the claim "PRIME reinforced the manageable safety profile demonstrated in PRIMA with no new safety signals for ZEJULA (niraparib)" appeared beneath the heading "PRIME Safety Profile". A similar structure to the PRIMA webpage followed, with a table displaying treatment emergent adverse events and the same boxed cautionary statement cited above.

The table included incidence rates (niraparib vs placebo) of:

- any Grade ≥3 TEAEs (54.5% vs 17.8%),
- serious TEAEs (18.8% vs 8.5%),
- treatment discontinuation (6.7% vs 5.4%),
- dose reduction (40.4% vs 6.2%),
- dose interruption (62.7% vs 19.4%), and
- treatment-related deaths (0.4% vs 0%).

In the niraparib group, the most common grade 3 or higher TEAEs included:

- anaemia (18.0%),
- neutropenia (17.3%),
- thrombocytopenia (14.1%), and
- leukopenia (6.7%).

Clauses 6.1 and 6.2

The Panel accepted GSK's submission that well-established oncology practice involved dose reduction, omission of dosage and/or discontinuation for the management of adverse events, and that these were addressed in the Zejula SPC.

The Panel considered that it was particularly important that material does not mislead regarding a medicine's safety profile, especially when associated with adverse reactions that were common and potentially serious.

Clause 6.1 required, among other things, that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous. They also must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. Clause 6.1 also required

material to be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine. Clause 6.2 required that any information, claim or comparison must be capable of substantiation.

The Panel noted that Zejula was associated with a significant proportion of Grade ≥3 TEAEs and that some of these adverse events were serious and led to treatment discontinuation. However, the complainant had not provided why the rate of discontinuation in either trial was unacceptable. The issue before the Panel was whether the claim “ZEJULA (niraparib) 1L monotherapy as a maintenance treatment demonstrated a manageable safety profile in two phase III clinical trials, PRIMA and PRIME”, was inaccurate due to certain adverse events leading to discontinuation, and misleading due to the lack of qualification regarding the discontinuation rates from each clinical trial.

The Panel relied upon the fact that the claim at issue appeared above two, prominent blue boxes with calls to action ("Learn More"). In the Panel’s view, the positioning and appearance of the buttons to the PRIMA and PRIME safety webpages which detailed the discontinuation rates, amongst other information, were such that a reader would likely be encouraged to access further information.

The Panel took account of the cumulative effect of the therapeutic area, intended specialised audience, the location of the claim in relation to the links to the PRIMA and PRIME trial safety data and the information provided on those subsequent pages. In the Panel’s view, the complainant had not established that the claim was inaccurate due to certain adverse events leading to discontinuation, nor that it was misleading or incapable of substantiation because the claim was not qualified by the discontinuation rates. On balance, the Panel concluded that the linked safety information sufficiently qualified the claim in question. The Panel therefore, on the specific allegations, ruled **no breach of Clause of 6.1 and Clause 6.2**.

Clause 5.1 and Clause 2

Based on its rulings of no breaches of the Code above, and in the absence of any other allegations from the complainant, the Panel did not consider that it had been established that GSK had failed to maintain high standards, nor that it had brought discredit upon, or reduced confidence in, the pharmaceutical industry. The Panel ruled **no breach of Clause 5.1 and Clause 2**, accordingly.

Complaint received **3 July 2024**

Case completed **28 May 2025**