CASE AUTH/3836/10/23

COMPLAINANT v GSK

Allegations about misleading information on a Zejula (niraparib) promotional webpage

CASE SUMMARY

This case was in relation to information about the management of adverse events included on a promotional webpage for Zejula.

The outcome under the 2021 Code was:

Breach of Clause 6.1	**Making a misleading claim**
Breach of Clause 5.1	**Failing to maintain high standards**

No Breach of Clause 11.2	**Requirement that a medicine must be promoted in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in its summary of product characteristics**
No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce the confidence in, the pharmaceutical industry**

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 about GSK from an anonymous, contactable complainant who described themselves as a health professional.

COMPLAINT

The complaint wording is reproduced below:

> "Claims on a Zejula webpage by GSK concerning adverse events management was misleading. The webpage is live at: [website link provided]. The webpage has the following reference code; [date and code provided] The headline claim on the webpage at the outset reads as the following 'If your patients have any side effects with ZEJULA (niraparib), they may be managed via dose interruption and modification1'. Further down on the same webpage, there was another claim which said 'Regularly monitoring your patient's complete blood count and blood pressure can help identify when dose modification may be required1*' In the SPC for Zejula 100mg tablets, there was

actually information that discontinuation was required for certain side effects as opposed to simply modification or interruption of dose to manage adverse effects. The following bits of discontinuation information were listed in the SPC: *If a patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, Zejula should be discontinued. *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. *Zejula should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy. The information in the SPC gave clear instruction to discontinue treatment during specific haemtaological [*sic*] and hypertensive adverse events. The promotional webpage in contrast only discussed management of adverse events via dose interupttion [*sic*] and modificitation [*sic*] but there was no mention of discontinuation. The impressions of such broad claims on the webpages would make the reader assume there was never any need for discontinuation and that simply modifying or interuptting *[sic]* the dosage would be sufficient which was not the case. Discontinuation was really important to protect patient safety and this should have been highligted *[sic]* clearly on a page about adverse events management. It is deeply troubling that such claims had gone live without challenge. Upon looking at the ABPI code, following clauses have not been adhered to – *6.1, 5.1 and 2."

When writing to GSK, the PMCPA asked it to consider the requirements of Clauses 11.2, 6.1, 5.1 and 2 of the Code.

GSK's RESPONSE

The response from GSK is reproduced below:

"GSK were extremely disappointed to receive a letter dated 11th October 2023 in which the PMCPA informed us of a complaint from an anonymous healthcare professional regarding the above. The PMCPA has asked us to consider clause 2, 5.1, 6.1 and 11.2 of the ABPI code practice (the code).

As referred to above, the complaint relates to a claim on the promotional webpage [job code provided], which the complainant alleges misled the audience by not including discontinuation as an option for adverse event (AE) management. The complainant has alleged breaches of clauses 2, 5.1 and 6.1 and the PMCPA have asked GSK to consider 11.2 in addition.

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 and following the complaint, we have conducted an internal review of the circumstances related to the post. GSK denies a breach of clauses 11.2 and 2 but acknowledge a breach of clauses 6.1 and 5.1.

Background

The webpage referred to is part of a more extensive promotional website called GSKPro which contains promotional information about all GSK products currently

marketed in the UK. Within the website there is a section dedicated entirely to the product Zejula (niraparib). The webpage in question is one of the sections within this.

The website can be accessed in two ways:

- directly by HCPs via a search engine, such as google, whereby the person trying to access the site would see a pop up on which they have to confirm they are an HCP as opposed to a member of the public.
- Promotional materials linking directly to the website.

The claim in question refers to the management of adverse events in the study PRIMA. PRIMA is a double-blind randomised phase 3 controlled trial designed to evaluate niraparib vs placebo maintenance therapy in women with stage III or IV ovarian cancer who have had a complete or partial response to platinum-based chemotherapy. Niraparib demonstrated a positive benefit/risk profile within the trial which was subsequently used to gain marketing authorisation for the product in the first line setting for the specific patient sub-group with ovarian cancer as above.

The claim in question is entitled 'PRIMA AE management' and is followed by the statement: 'If your patients have any side effects with Zejula (niraparib) they may be managed via dose interruption and modification.' The page leads on to the visual representations of complete blood monitoring and blood pressure monitoring with a title claim stating 'regularly monitoring your patients' complete blood count and blood pressure can help identify when dose modification may be required' followed by a statement below the visual representation saying: '*Please refer to the SmPC when making prescribing decisions. The information provided here is to supplement understanding rather than replace the advice in the SmPC*.' GSK has described in detail our response to the specific clauses the PMCPA has asked us to consider below.

The aim of the page was to inform healthcare professionals that there is an option for dose interruption and modification of niraparib before reaching the decision to discontinue entirely. The use of regular monitoring supports a healthcare professional with the decision making involved. Advanced ovarian cancer is treated by specialists in their field who, we contend, would also be aware that discontinuation of any of the treatments they use (including niraparib) when experiencing adverse events is an option, due to the nature of the medicines they use as well as their potencies and side effect profiles. The SmPC for niraparib states very clearly in Section 4.2: Posology and method of administration that: '*Treatment with Zejula should be initiated and supervised by a physician experienced in the use of anticancer medicinal products*.'

GSK processes and structure

GSK has what we consider to be robust processes and structures in place with regards to the approval of materials in line with not just the code, but also GSK's own code and other UK rules and regulations. Every employee involved in any aspect of copy approval is expected to have trained on the mandatory GSK copy approval SOP. In addition, every individual brand team within GSK has in place a regular forum for decision and agreement (FDA) where the team, including medical affairs and commercial, can discuss materials in development and requiring copy approval, in order to align together. For situations where there is no agreement e.g. for a particular

claim, there is a clear and well-established route of escalation by the medical signatory and/or wider team.

To enable on-going knowledge of the code, GSK run a monthly code forum meeting in which code cases are presented and discussed as well as other compliance/governance issues which need highlighting to the wider team. The meeting is intended for all medical signatories, commercial reviewers, content owners and anyone else who is interested in attending, with a good turnout at each meeting. The slide decks presented are stored on our internal governance and process platform which is available to all GSK UK employees.

In addition, GSK also holds a six-weekly signatory forum for all medical signatories and commercial reviewers, where team members can raise any code issues for discussion by a larger group, including many experienced signatories. There is very good attendance at this meeting also.

Additionally, GSK has a fair and objective process for assessing and validating not only medical signatories, but also commercial reviewers, whose role is to provide commercial overview of all promotional and relevant non-promotional copy approval jobs for appropriateness, (including the more obvious aspect of the code), suitability and strategic importance. This assessment involves 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 and, in the case of medical signatories, been mentored for a period of time by another experienced medical signatory until deemed ready for the assessment to become a signatory.

Clause 6.1

GSK endeavours to hold itself to the highest standards possible and in this respect, we acknowledge that further information should have been included on the webpage around the specific scenarios for which niraparib should be discontinued, as per the SmPC. However, GSK contend that the overall information provided on the webpage, and indeed the entire promotional website, is balanced, fair, objective, and unambiguous and is based on the most up-to-date evidence, which is reflected accurately and clearly.

We also contend that none of the information provided, undermines the ability of recipients to form their own opinion of the therapeutic value of niraparib. As per the complainant's allegation, what is missing from the webpage is additional information about the circumstances in which niraparib should be discontinued in the case of certain AEs. GSK has clearly emphasised the importance of monitoring and has also highlighted the need for treatment interruption or dose modification with niraparib if adverse events (AEs) occur. It is important to point out that not all AEs require discontinuation, and that the management of AEs is dependent upon close monitoring and responding appropriately to the results by the treating HCP.

There is a clear reference on the webpage to the SmPC for further information including the details about what HCPs should do following treatment interruption or modification is dependent on the specific AE or circumstances. Treatment

discontinuation is one of the options for specific scenarios, but GSK contend that this decision can only be made by HCPs after first interrupting treatment and subsequently monitoring or investigating patients further depending on their symptoms, abnormal examination, or test result. Indeed, none of the conditions for which niraparib treatment should be discontinued can be diagnosed without monitoring, either before or during the dose interruption phase. GSK has clearly emphasised the importance of both monitoring, and dose modification/interruption on the webpage. However, we acknowledge that the webpage can be improved to be even clearer, and GSK therefore acknowledge a breach of clause 6.1.

Clause 5.1

In accepting that a breach of clause 6.1 has occurred as above, GSK accept that high standards have not been maintained and we therefore also acknowledge a breach of clause 5.1.

Clause 11.2

The PMCPA has asked us to consider clause 11.2 in our response. GSK contends that the omission of information about specific scenarios for the discontinuation of treatment with niraparib is not inconsistent with the terms of its marketing authorisation and neither is it the promotion of an indication/s which are not covered by the marketing authorisation. GSK contends that it is additional information for the management of some adverse events, which may be of use to HCPs involved in the ongoing treatment of patients already deemed to be clinically eligible for niraparib. GSK therefore deny breaching clause 11.2.

GSK response to potential breach 2

The PMCPA have also asked GSK to consider clause 2. As mentioned above, GSK acknowledges that the information about the specific circumstances for some AEs for which niraparib should be discontinued should have been included on the webpage in question. As mentioned above, GSK is already in the process of updating our materials to provide greater clarity about the treatment of AEs. The aim of the webpage was to supplement understanding and help relevant HCPs to get an overview of how to manage their patients on niraparib. The safety information provided on the webpage was not intended to replace the SmPC, which contains significantly more detailed information and which GSK believes should be the primary source of information for HCPs to refer to, but rather to summarise the information in it. For this reason, the webpage highlights the importance of the SmPC as the main source of information in the form of the statement under the visual image about blood count and blood pressure monitoring mentioned above.

The webpage is explicit about the need for blood count and blood pressure monitoring to help identify when dose modification may be required, as well as providing other, extensive safety information from the key trials including the discontinuation rates.

GSK contends that the three specific AEs mentioned by the complainant are only identifiable by the regular monitoring of blood count and blood pressure. As already mentioned above, the need for this is clearly highlighted on the webpage. The SmPC

for niraparib also contains additional information about dose modification including the doses to use in given circumstances. Crucially, the SmPC states that for AEs, the first step is to interrupt treatment which has been mentioned on the webpage. The SmPC advises that if the adverse event does not settle in 28 days after the dose interruption (i.e., the patient needs to be monitored during that time), niraparib should be discontinued. The SmPC then goes into much greater detail about specific AEs (including the three mentioned by the complainant) which require the treating HCP to assess several parameters such as blood counts, blood pressure, adverse event severity grading etc.to help decide what course of action they should take next. GSK contend that because of the level of complexity of managing AEs, HCPs would refer to the SmPC before making any further decisions following dose interruption and would not rely solely on a pharmaceutical company website. Indeed, as mentioned above, GSK has reinforced this by means of a statement on the webpage.

GSK acknowledge and agree that a breach of clause 2 is reserved for special sanction when significant failings have been identified, including a risk to patient safety. While GSK acknowledge that more clarity could have been provided about the specific AEs which require discontinuation of niraparib, and in that regard have not upheld the high standards to which we hold ourselves, we contend that the information provided on the webpage was still adequate to ensure that HCPs acting on it would have managed their patients' AEs appropriately, including discontinuing niraparib treatment where necessary. We therefore contend that there was no actual risk to patients by the omission of the information about discontinuation. However, we acknowledge that we can improve the webpage and are in the process of doing so.

As also described above, GSK has in place a robust structure and processes to try to ensure high standards are maintained with regards to the creation, review and approval and certification of promotional materials. For these reasons, GSK deny a breach of clause 2.

Summary

GSK take responsibility of abiding by the letter and the spirit of the code extremely seriously. We also hold to the principle of continuous improvement when things are identified which can be improved in our materials. As laid out in our detailed response above GSK acknowledge a breach of clauses 6.1 and therefore clause 5.1, because we believe that our materials can be improved on the back of this complaint and the subsequent internal review. We deny breaches of clause 11.2 and 2 however, for the rationale explained above."

PANEL RULING

The Panel noted Zejula (niraparib) was indicated as monotherapy for the maintenance treatment of adult patients with:

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

- 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,

and that Section 4.2 of the summary of product characteristics required that treatment with Zejula was initiated and supervised by a physician experienced in the use of anticancer medicinal products.

The Panel noted the webpage at issue was part of the Zejula section of the larger GSKPro promotional website. The Zejula section contained subsections accessed by tabs at the top of each webpage which were labelled, “Home”, “PRIMA & PRIME”, “EFFICACY”, “SAFETY PROFILE”, “QOL” (quality of life), “DOSING” and “More”. The allegations concerned a webpage titled, “PRIMA AE management”, within the safety profile subsection.

The Panel considered the layout of the webpage. Beneath the heading “PRIMA AE management” was the claim “If your patients have any side effects with ZEJULA (niraparib), they may be managed via dose interruption and modification”. Beneath this were two graphics titled “Regularly monitoring your patient’s complete blood count and blood pressure can help identify when dose modification may be required”. One graphic illustrated the monitoring schedule for complete blood count monitoring and the other the schedule for blood pressure monitoring. Immediately below, in a smaller font, was the statement “Please refer to the SmPC when making prescribing decisions. The information provided here is to supplement rather than replace advice in the SmPC”. The footnote associated with the title of the graphics stated “Dose reduction includes both direct dose reduction and dose reduction following treatment interruption”. Links to the prescribing information and adverse event reporting were located near the top of the webpage. A link to the PRIMA safety profile appeared towards the bottom of the webpage.

The complainant alleged that the claims “If your patients have any side effects with ZEJULA (niraparib), they may be managed via dose interruption and modification” and “Regularly monitoring your patient’s complete blood count and blood pressure can help identify when dose modification may be required” were broad and could give the impression there was never any need for discontinuation of treatment and that dose modification or dose interruption was sufficient for the management of adverse events associated with Zejula treatment, which was not the case.

The Panel noted section 4.2 of the summary of product characteristics, dose adjustments for adverse reactions, stated:

> “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.”

In addition, section 4.4 of the summary of product characteristics, special warnings and precautions, included several circumstances when Zejula should be discontinued. These were:

- severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption
- if MDS/AML is confirmed, Zejula treatment should be discontinued, and the patient treated appropriately
- hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.
- in Posterior Reversible Encephalopathy Syndrome (PRES), it is recommended to discontinue Zejula and to treat specific symptoms including hypertension.

The Panel noted the content of the PRIMA subsection as a whole and considered the immediate and overall impression created by the "PRIMA AE management" webpage as a standalone page and also within the context of the other webpages in the subsection.

The Panel noted that the long-term 3.5-year median follow up safety results for the study in both the Zejula and placebo arms and for the overall population and the individualised starting dose population were shown on the four webpages immediately preceding the one at issue. The first two of which showed the rates for dose reduction, interruption, discontinuation and death resulting from a treatment emergent adverse event while the webpages immediately before the one at issue contained two forest plots showing the rates of treatment emergent adverse events occurring in 20% or more in each cohort of patients.

GSK submitted that the "PRIMA AE management" webpage emphasised the importance of monitoring and highlighted the need for treatment interruption or dose modification if adverse events occurred. It also submitted that not all adverse events required discontinuation and the management of adverse events was dependent on health professionals closely monitoring patients and responding appropriately. In this regard the Panel noted the statement directing health professionals to refer to the summary of product characteristics when making prescribing decisions was directly below the graphics displaying the monitoring schedules for complete blood count and blood pressure.

Notwithstanding that Zejula prescribers were experienced specialists in the field of cancer treatment and that important safety information was available on the preceding pages, the Panel considered it was well established that each webpage should be capable of standing alone.

Clause 6.1 required, among other things, that claims must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis and material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine.

The Panel noted the aim of the webpage was to supplement understanding and provide an overview of how health professionals should manage patients on Zejula; however, the webpage was headed "AE management" and thus could be expected to highlight the full range of actions mentioned within the summary of product characteristics to manage adverse events. The Panel considered that a statement directing health professionals to refer to the summary of product characteristics when prescribing was not sufficient to alert viewers to the need for discontinuation in certain circumstances. In the Panel's view, the webpage created a misleading impression by failing to highlight that, for some patients, management of adverse events might require discontinuation of treatment rather than modification of the dose. The Panel ruled a **breach of Clause 6.1**.

The Panel noted the allegations related to the appropriate use and discontinuation of a medicine. The Panel considered the omission of information related to safety demonstrated that GSK had failed to maintain high standards and it ruled a **breach of Clause 5.1**.

Both breaches were acknowledged by GSK.

The Panel noted that Clause 11.2 had been raised by the case preparation manager. While noting its comments above regarding the webpage and the provision of incomplete information, the Panel considered, on balance, that the omission of information about treatment discontinuation, did not mean that the webpage as a whole was inconsistent with the summary of product characteristics or that Zejula had been promoted outside the terms of its marketing authorisation. Accordingly, the Panel ruled **no breach of Clause 11.2**.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The Panel considered its breach rulings above dealt adequately with the matters raised. Accordingly, the Panel did not consider that the circumstances of this particular case warranted a ruling of a breach of Clause 2. **No breach of Clause 2** was ruled.

Complaint received **10 October 2023**

Case completed **13 September 2024**