CASE AUTH/3918/6/24

COMPLAINANT v JAZZ PHARMACEUTICALS UK

Allegations about presentation in a promotional video

CASE SUMMARY

This case was in relation to allegations relating to a promotional presentation on Epidyolex (cannabidiol).

The outcome under the 2021 Code was:

Breach of Clause 2	**Bringing discredit upon, and reducing confidence in, the pharmaceutical industry**
Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 6.1 (x2)	**Making a misleading claim**

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 claims/information/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 Jazz Pharmaceuticals UK was received from an anonymous, contactable complainant who described themselves as a health professional.

The complainant has now become non-contactable.

COMPLAINT

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

> "Epidyolex promotional presentation funded by Jazz Pharma aimed at UK HCPs which contained patient case studies did not discuss contraindications around hepatic monitoring. The presentation gave a brief overview of hepatic monitoring at the start of the presentation (20 to 29 seconds). During this hepatic monitoring information, the contraindication where patients with transaminase elevations greater than 3 times the ULN and bilirubin greater than 2 times the ULN (Section 4.3 SmPC) should not be given Epidyolex, was missing. In the context of presenting patient case studies on initiation and maintenance therapy with Epidyolex, presenting contraindications around

hepatic transaminases were necessary to protect patient safety especially as hepatic monitoring was presented at start of presentation. The 2 presentations by [Speaker 1] and [Speaker 2] did not discuss the contraindication around hepatic transaminase elevations either despite the case studies discussing the initiation and continuation of Epidyolex. In the summary presented by [Speaker 2] at 38:23 it was claimed Epidyolex has a manageable safety profile as her last summary point. This is misleading as pneumonia and hepatic enzyme elevations (section 4.3 of SMPC) are common side effects which would require withdrawal of Epidyolex and not management. The presentation directly breached clauses 6.1 & 6.2 & 5.1 & 2 of the ABPI code."

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

JAZZ'S RESPONSE

The response from Jazz is reproduced below:

"Thank you for your letter of 7th June 2024, in which you notified us of a complaint from an unnamed Healthcare Professional relating to an Epidyolex educational promotional presentation. We were requested to respond to this matter with consideration to the Clause requirements of 6.1, 6.2, 5.1 and 2, as cited by the complainant.

The specific concerns raised by the complainant are outlined as follows:

- During the hepatic monitoring information, the contraindication where patients with transaminase elevations greater than 3 times the ULN and bilirubin greater than 2 times the ULN (section 4.3 Summary of Product Characteristics (SmPC)) should not be given Epidyolex, was missing.

- Two of the individual presentations included in the presentation did not discuss the contraindication around hepatic transaminase elevations despite the case studies discussing the initiation and continuation of Epidyolex

- In one of the presentations, it was claimed Epidyolex had a manageable safety profile and that this is misleading as pneumonia and liver enzyme elevations would require withdrawal of Epidyolex, not management.

In response to these allegations, we provide the following information and explanations.

As part of the commitment to help improve patient care in the specialist management of specific developmental and epileptic encephalopathies (DEEs) and associated comorbidities, Jazz provided an educational promotional presentation for health care professionals. It is important to note that the two presentations referred to by the complainant were part of the same audio-visual presentation that was certified . The overarching narrative of the presentation was the management of DEEs, with the majority of the slides given over to this subject. Of the slides specifically referring to Epidyolex, 40% cover safety aspects related to Epidyolex use.

The complainant alleges that 'During this hepatic monitoring information, the contraindication where patients with transaminase elevations greater than 3 times the

ULN and bilirubin greater than 2 times the ULN (Section 4.3 SmPC) should not be given Epidyolex was missing'.

From the outset of the presentation, there is a clear reference, that prior to starting treatment with Epidyolex, serum transaminases (ALT and AST) and total bilirubin levels should be obtained, together with information that Epidyolex can cause dose-related elevations of liver transaminases (ALT and/or AST) along with the details of the monitoring requirements indicated. Furthermore, details of the intensified monitoring schedule for patients who receive conjunctive valproate treatment or with elevated baseline ALT or AST is also included. A slide showing commonly reported adverse events from the clinical trials is shown which includes raised liver enzymes as a common adverse event along with several other adverse events.

The presentation is discussing case studies in which there were no concerns about liver abnormalities in the individual patients. Despite this, as Jazz takes patient safety and the requirements of the ABPI Code (the 'Code') very seriously, we briefed the speakers to include the reference to all commonly reported adverse events and also reviewed and approved the slides with these concerns in mind. As the presentation was focused on management of the presented patient cases, there was no specific requirement to cover every adverse event and contraindication.

As previously described, the presentation contained information on dose related elevations of transaminases and monitoring requirements for transaminases and bilirubin and in that respect safety data was presented to the audience. The presentation provided information to support responsible prescribing, including the clinical considerations for prescribing, safety considerations, and adverse events. We believe we have included necessary safety data. With this regard we assert that the content of the material is consistent with the requirements of Clauses 6.1 and 6.2 and that high standards were upheld.

The complainant alleges that stating that Epidyolex has a manageable safety profile is 'misleading as pneumonia and hepatic enzyme elevations (section 4.3 of SPC) are common side effects which would require withdrawal of Epidyolex and not management'. However, the complainant is incorrect: the SPC does not require that a patient is stopped from being treated with Epidyolex in the case where they have either pneumonia or hepatic enzyme elevations. Section 4.4 of the SPC details management of hepatocellular injury and outlines several options for managing cases of elevations of transaminases; these include dose adjustment or discontinuation of concomitant medications and discontinuation or dose reduction of cannabidiol. It is also stated that in about one third of cases, transaminase elevations resolved during continued treatment with cannabidiol without dose reduction. Thus, it is clear that liver enzyme elevations do not always, require withdrawal of Epidyolex, but that they can be managed.

It is also alleged that development of the adverse event of pneumonia would require withdrawal, not management, of Epidyolex. This is factually incorrect; the SPC does not require withdrawal of Epidyolex if a patient develops pneumonia. In nowhere in the SPC, is a dose adjustment and/or discontinuation of Epidyolex mentioned for pneumonia.

Thus, it is clear that the guidance from the Epidyolex SPC does not require that physicians reduce or discontinue the use of cannabidiol in patients with pneumonia and hepatic transaminase elevations. Rather it equips the physician with information and a suggestion of various courses of action to be considered including continuing the treatment.

Prescribing information is also shown in the presentation which gives details of the requirement for increased frequency of monitoring liver function in cases where cannabidiol and valproate are used together, and guidance about when to interrupt or discontinue treatment. The contraindication statement for transaminase levels >3 x ULN and bilirubin >2 x ULN is included within the Prescribing Information.

All information in the presentation is capable of substantiation and in line with the SPC, so we refute a breach of clause 6.2. As such, high standards were upheld.

The complainant alleges a breach of Clause 5.1. We refute this allegation on the basis that Jazz has maintained high standards throughout this activity. Jazz reviewed and certified all materials and provided a clear briefing to speakers in advance of the recording, specifically briefing on the need to provide balanced information. In this instance materials were certified by a GPhC registered Pharmacist Signatory.

The complainant alleges a breach of Clause 2 in relation to the allegations. Clause 2 is a sign of particular censure and is reserved for such circumstances, we believe that this presentation has been prepared and presented in line with Clauses 6.1. 6.2 and 5.1 of the Code and therefore we refute a breach of Clause 2.

At Jazz, we take our commitment to upholding industry standards through our activities and interactions seriously, and I hope that the information provided will lead to resolution of the allegations made in this case."

PANEL RULING

The complaint concerned a promotional presentation on Epidyolex, which was indicated for use as an adjunctive therapy of seizures associated with Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS) or tuberous sclerosis complex (TSC). The video presentation was funded by Jazz Pharmaceuticals who submitted that it was aimed at UK health professionals. The video was 39 minutes 35 seconds long and featured presentations by three speakers. The Panel interpreted the complaint as making three separate allegations:

1. Two introductory slides (at 18-29 seconds, before the presentations began), discussed dose adjustments for patients with hepatic impairment, but did not include the following information from Section 4.3 of the Summary of Product Characteristics (SPC): the contraindication where patients with transaminase elevations greater than three times

the Upper Limit of Normal (ULN) and bilirubin greater than two times the ULN should not be given Epidyolex.

2. Two of the individual presentations did not discuss the contraindication around hepatic transaminase elevations despite the case studies discussing the initiation and continuation of Epidyolex.

3. At 38 minutes 23 seconds, the claim that Epidyolex had a manageable safety profile was misleading because pneumonia and liver enzyme elevations would require withdrawal of Epidyolex; not just management.

The Panel noted Jazz's submission that the presentation video was created for health professionals to improve patient care in the specialist management of specific developmental and epileptic encephalopathies and associated comorbidities. Jazz commented that the complainant referred to two presentations in their allegations, however they were part of the same audio-visual presentation.

The Panel noted the hepatic considerations for Epidyolex in the SPC included that patients with hepatic impairment were mentioned as a special population in Section 4.2 which stated:

> 'Cannabidiol does not require dose adjustment in patients with mild hepatic impairment (Child-Pugh A). Caution should be used in patients with moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C). A lower starting dose is recommended in patients with moderate or severe hepatic impairment.'

In addition, Section 4.4 contained the following special warning and precaution for use in patients with hepatic impairment:

> 'In general, transaminase elevations of greater than 3 times the ULN in the presence of elevated bilirubin without an alternative explanation are an important predictor of severe liver injury. Early identification of elevated transaminase may decrease the risk of a serious outcome. Patients with elevated baseline transaminase levels above 3 times the ULN, or elevations in bilirubin above 2 times the ULN, should be evaluated prior to initiation of cannabidiol treatment. Prior to starting treatment with cannabidiol, obtain serum transaminases (ALT and AST) and total bilirubin levels.'

Section 4.3 of the SPC (Contraindications), stated that Epidyolex was contraindicated in patients with transaminase elevations greater than three times the ULN and bilirubin greater than two times the ULN.

<u>Allegation 1 – the absence of the contraindication in the introductory slides at 20-29 seconds</u>

The Panel considered two slides included in the presentation at 20-29 seconds:

1. The first slide was titled, 'GB indication and dosing for Epidyolex (cannabidiol) 100mg/mL oral solution (1/2)'. The Panel noted that this was one of two slides referring to hepatic monitoring whilst a patient was having Epidyolex treatment. This slide contained a banner below the two indications which read 'Prior to starting treatment, obtain serum transaminases (ALT and AST) and total bilirubin levels' and several bullet points below the dosing table referred to routine monitoring and intensive monitoring.

The second bullet point read 'Epidyolex can cause dose-related elevations of liver transaminases.' The slide did not however, refer specifically to patients presenting with transaminase elevations greater than three times the ULN and bilirubin greater than two times the ULN and the contraindication specified in sections 4.3 and 4.4 of the SPC.

2. The second slide was similarly titled and referred to dose adjustments in patients presenting with moderate and severe hepatic impairment. The columns headed 'Maximal recommended dose for LGS and DS' and 'Maximal recommended dose for TSC', within the severe hepatic impairment row contained an asterix after the dose. The asterix referred to, was directly below the dosing table, and read 'Higher doses of cannabidiol may be considered in patients with severe hepatic impairment where the potential benefits outweigh the risks.' This slide also commented on hepatic impairment by stating in relation to dose adjustment that, 'Caution should be used in patients with moderate or severe hepatic impairment' and 'a lower starting dose is recommended in patients with moderate or severe hepatic impairment. The dose titration should be performed as detailed above and in the SmPC.'

The Panel noted a reference to the prescribing information and SPC was provided on both slides. However, the Panel also considered that the slides should be capable of standing alone in relation to the requirements of the Code.

The Panel noted Jazz's submission that details of the intensified monitoring schedule for patients who receive conjunctive valproate treatment or with elevated baseline ALT or AST was included within the presentation. The Panel considered that it was misleading to state that low dosing was indicated for patients 'with moderate or severe liver impairment' without also stating that Epidyolex was contraindicated in severe hepatic impairment. AST/ALT values more than twice the ULN would also include patients with severe hepatic impairment. Nowhere on either slide did it state that Epidyolex was contraindicated in severe hepatic impairment.

The Panel considered that whether a contraindication needed to be highlighted within a particular section of promotional material, in addition to its requirement to be included within the prescribing information that was required on all promotional material, depended on a consideration of all of the circumstances including the nature of the contraindication and the content, layout, audience and intended use of the material.

Given the information on monitoring of liver transaminases and hepatic impairment within the 'Indications and dosing for Epidyolex' slides, the Panel considered it likely that a health professional would expect and assume that all the relevant information in relation to hepatic impairment would be stated in the slide. Given that information had not been included in this case, the Panel considered that this gave a misleading impression, which was compounded by the reference to low dosing in patients with AST/ALT values more than twice the ULN, not including further clarification that it was contraindicated in patients with transaminase elevations greater than three times the ULN and bilirubin greater than two times the ULN. The Panel considered that by providing some, but not all, of the relevant information in relation to hepatic impairment in a section of the presentation which was intended to advise health professionals on considerations when using the medicine, the slides were misleading and a **breach of Clause 6.1** in relation to each was ruled.

Allegations 2 – the absence of contraindications from the case studies

The Panel noted the allegation that the case studies provided by two of the presenters also did not refer to the contraindication around hepatic transaminase elevations, despite these case studies discussing the initiation and continuation of Epidyolex. The Panel noted that the two sections were titled:

- A whole-patient approach to DEE management: A paediatric neurologist's perspective
- A whole patient approach to DEE management: An adult neurologist's perspective

For the same reasons as provided above in relation to allegation 1, the Panel concluded that the case studies ought to have included references to the contraindication around hepatic transaminase elevation, but they did not do so. The Panel therefore ruled a **breach of Clause 6.1**.

Allegation 3 – the reference to a manageable safety profile was misleading

The Panel considered the presentation video at 38 minutes and 23 seconds, where the second speaker presented a summary slide within the section titled 'A whole patient approach to DEE management: An adult neurologist's perspective'.

The slide was headed 'Summary' and featured four statements, the last of which stated:

'Epidyolex (regulatory-approved CBD medication) has demonstrated improvements in seizure- and non-seizure-related outcomes with a manageable safety profile for patients with LGS and DS.'

The complainant alleged that this summary point was misleading because pneumonia and hepatic enzyme elevations were common side effects which would require complete withdrawal of Epidyolex, not just management. However, the Panel noted that the complainant was incorrect on this point and the SPC did not require a patient's treatment to be completely discontinued in this instance. Section 4.8 of the SPC (undesirable effects) referred to pneumonia as a common adverse event occurring with Epidyolex treatment; but there was no reference to withdrawal or management of Epidyolex in these circumstances. The complainant's allegation on this point was not well-founded and the Panel therefore ruled **no breach of Clause 6.1.**

The Panel noted that Clause 6.2 had been cited, but did not consider that the complainant had alleged that the subject matter of the complaint could not be substantiated and so the Panel ruled **no breach of Clause 6.2**.

Clause 5.1 and Clause 2

The Panel noted its rulings of breaches of the Code above, including in relation to matters of patient safety, and considered that Jazz had failed to maintain high standards and a **breach of Clause 5.1** was ruled.

Clause 2 was a sign of particular censure and was reserved for such use. The supplementary information to Clause 2 included prejudicing patient safety as an example of an activity that was likely to be in breach of this clause.

The Panel considered that patient safety was of the utmost importance and that health professionals should be able to rely on materials produced by companies to be complete and unambiguous in this regard. The Panel considered that by providing some, but not all, of the relevant information in relation to hepatic impairment in a presentation which was intended to advise health professionals on indications and dosing when using the medicine, was such that Jazz had reduced confidence in, and brought discredit upon, the industry and a **breach of Clause 2** was ruled.

Complaint received **2 June 2024**

Case completed **19 May 2025**