CASE AUTH/2871/8/16

VOLUNTARY ADMISSION BY JANSSEN

Pre-licence promotion

Janssen-Cilag voluntarily admitted breaches of the Code as a Crohn's disease awareness campaign initiated and approved by the Janssen European team was used in the UK and amounted to pre-licence promotion.

The campaign consisted of an email sent on 2 June and images and news headline links made available to Gastroenterology members 29 June – 29 July.

The email was headed 'Developed under the direction and sponsorship of Janssen Pharmaceutical Companies' followed by 'Crohn's. Let's re-write their story'. The next heading was 'Relapse' where 'lapse' had been crossed out and 'mission' added ie 'Relapse' had been amended to 'Remission' followed by 'A disease with many unknowns, has many treatment challenges'. The email stated that there was no known cause or cure for Crohn's disease but with better understanding of the pathophysiology the ambition of treatment was to move from short-term symptom control to more targeted long term disease modification. There were high treatment failure rates with existing biological therapies (40% of patients did not respond to anti-tumour necrosis factor (TNF)). Patients needed more effective treatment options to improve overall disease management and optimise outcomes. The email then referred to the need to understand the disease pathway at the molecular level followed by 'Janssen has been working tirelessly to improve the way Crohn's is managed' and that the company was 'committed to discovering pioneering treatments for Crohn's disease'. Janssen introduced the first anti TNF in 1998 and continued to lead the way. It had expanded its research focus to include other targets now known to drive inflammation and autoimmune processes. Working with others Janssen was committed to developing new tailored therapeutic options 'in order to provide the right treatment for the right person in every part of the world'.

The email concluded with a box headed 'Learn more about Janssen's commitment to Crohn's management' with three links to the results of studies of ustekinumab in Crohn's Disease.

The last sentence below the references was 'This promotional communication is provided by [named third party]'.

The images and news headline links were made available to Gastroenterology members accessing the Medscape website; the alerts appeared adjacent to other news headlines at that time. During that period, the headline 'Remission: the goal for all patients with Crohn's disease ' followed by 'information from industry' were shown in three forms, desktop, news section and home page versions, to UK gastroenterologists. A link from the news headline took readers to the same email content 'Remission: Mapping new pathways for Crohn's disease treatment'.

Stelara (ustekinumab) was currently indicated for the treatment of moderate to severe plaque psoriasis and for the treatment of adult patients with psoriatic arthritis. Stelara did not yet have a licensed indication for the treatment of Crohn's disease. In November 2015 Janssen sought approval from the European Medicines Agency for this indication.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Janssen.

The detailed response from Janssen is given below.

The Panel noted that Janssen in Europe had emailed UK health professionals without the involvement of Janssen UK which had therefore not certified the materials. The email could also be accessed from advertisements which read 'Remission: the goal for all patients with Crohn's disease. Information from industry'. These advertisements were accessible to members of Medscape who were gastroenterologists.

The Panel noted that there appeared to be a serious error in that the relevant Janssen EMEA standard operating procedure (SOP) required materials to be sent to the local company for approval prior to use and this had not happened. Janssen UK submitted that this was due to human error. This appeared to the Panel to be conduct that fell short of competent care.

The Panel considered that the email was clearly promotional. It discussed the treatment of disease pathways of Crohn's disease and provided links to results of studies using Stelara for Crohn's Disease. It mentioned that Janssen was committed to discovering pioneering treatments for Crohn's disease and the need for more effective treatment options. Stelara was not indicated for Crohn's Disease. The advertisements were linked to the email and thus were also promotional. The Panel ruled a breach of the Code as the material was inconsistent with the Stelara summary of product characteristics (SPC) as acknowledged by Janssen UK. The material had not been certified and a breach of the Code was ruled as acknowledged by Janssen.

The Panel ruled that high standards had not been maintained in breach of the Code as acknowledged by Janssen UK. It considered that by promoting an unlicensed indication and failing to certify the material it brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

Janssen-Cilag Ltd voluntarily admitted breaches of the Code as a Crohn's disease awareness campaign initiated and approved by the Janssen European team amounted to pre-licence promotion. The regional campaign in question was delivered to health professionals, including the UK and therefore Janssen-Cilag believed it might fall within the scope of the ABPI Code.

The campaign consisted of an email (Ref PHEM/STE/0116/0002d) sent on 2 June and images and news headline links made available to Gastroenterology members 29 June – 29 July.

The email was headed 'Developed under the direction and sponsorship of Janssen Pharmaceutical Companies' followed by 'Crohn's. Let's re-write their story'. The next heading was 'Relapse' where 'lapse' had been crossed out and 'mission' added ie 'Relapse' had been amended to 'Remission' followed by 'A disease with many unknowns, has many treatment challenges'. The email stated that there was no known cause or cure for Crohn's disease but with better understanding of the pathophysiology the ambition of treatment was to move from short-term symptom control to more targeted long term disease modification. There were high treatment failure rates with existing biological therapies (40% of patients did not respond to anti-tumour necrosis factor (TNF)). Patients needed more effective treatment options to improve overall disease management and optimise outcomes. The email then referred to the need to understand the disease pathway at the molecular level with details of cytokine activity including proinflammatory effector cytokines such as IFN, TNF and IL6. This was followed by 'Janssen has been working tirelessly to improve the way Crohn's is managed' and that the company was 'committed to discovering pioneering treatments for Crohn's disease'. Janssen introduced the first anti TNF in 1998 and continued to lead the way. It had expanded its research focus to include other targets now known to drive inflammation and autoimmune processes. Working with others Janssen was committed to developing new tailored therapeutic options 'in order to provide the right treatment for the right person in every part of the world'.

The email concluded with a box headed 'Learn more about Janssen's commitment to Crohn's management' with three links to the results of studies of ustekinumab in Crohn's Disease.

The last sentence below the references was 'This promotional communication is provided by [… named third party service].

The images and news headline links were made available to Gastroenterology members accessing the Medscape website; the alerts appeared adjacent to other news headlines at that time. During that period, the headline 'Remission: the goal for all patients with Crohn's disease ' followed by 'information from industry' were shown in three forms, desktop, news section and home page versions, to UK gastroenterologists. Clicking on the news headline took readers to the same email content 'Remission: Mapping new pathways for Crohn's disease treatment'.

Stelara (ustekinumab) was currently indicated for the treatment of moderate to severe plaque psoriasis and for the treatment of adult patients with psoriatic arthritis. Stelara did not yet have a licensed indication for the treatment of Crohn's disease. In November 2015 Janssen sought approval from the European Medicines Agency for this indication.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Janssen.

VOLUNTARY ADMISSION

Janssen stated that the Janssen European business was affiliated to Belgium-based Janssen Pharmaceuticals NV, not part of the Janssen UK legal entity. One of the European approvers for the campaign material resided in the UK, although he/she was neither employed by Janssen in the UK, nor based at Janssen UK headquarters.

While the primary focus of the campaign was on the role of the disease pathway in the progression and management of the condition, it incorporated click-through functionality which included links to on-line publications of previous legitimate scientific exchange relating to Stelara in Crohn's Disease, namely:

a) United European Gastroenterology Week (UEGW) congress summary report, featuring a brief summary of the Stelara Crohn's Disease phase 3 induction study, UNITI-2.

b) European Crohn's and Colitis Organisation (ECCO) congress abstract relating to a retrospective observation study of Stelara in Crohn's Disease patients in French tertiary centres.

c) Gastroenterology.org abstract of the Stelara Crohn's Disease phase 3 maintenance study, IM-UNITI.

During the course of regular monthly teleconferences with Janssen European colleagues in April and May 2016, a UK manager was informed that a disease awareness campaign was among a range of materials being developed in preparation for launch in the fourth quarter of 2016. However, in keeping with usual practice, the expectation was that these campaign materials would be rolled out to the local operating companies for amendments and copy approval to be completed prior to any local implementation. There was no further communication detailing the intended extent or time line for European roll-out of the campaign or that UK clinicians were to be included, nor were materials and references supplied to the UK team to enable local approval and certification prior to use.

On the evening of 15 August, the UK marketing team received an email from a European manager reporting that the disease awareness campaign had been deployed and it was then evident that the campaign had been sent to gastroenterologists practising in the UK. On further investigation Janssen-Cilag identified the following:

- An email (subject header 'Remission: Mapping new pathways for Crohn's disease treatment') was sent on 2 June 2016 by the third party, to its registered members. These included gastroenterologists in the UK, who had all opted-in to receive promotional email communications. 2,303 emails were sent to UK health professionals, of which 414 were opened. There were only 4 occasions on which health professionals followed the links to the additional information which pertained to Stelara specifically.

- During a 30-day period from 29 June to 29 July 2016 the three 'news headline' images were available to Gastroenterology members accessing the Medscape environment, adjacent to other news headlines at the time. Customers clicking on this news headline were taken to the same email content outlined above. During that period, the following headlines were shown to 1,042 UK gastroenterologists, of whom 345 accessed the email content. There were only 10 occasions on which health professionals followed the links to the additional information which pertained to Stelara specifically.

The number of click throughs from the email and alert to one of the three studies was provided and were 4 or fewer.

Janssen submitted that the above activities represented promotion outside the particulars listed in the Stelara summary of product characteristics (SPC) (Clause 3.2) failure to maintain high standards at all times (Clause 9.1) and failure to obtain UK certification of promotional materials distributed to UK health professionals (Clause 14.1 – albeit the European team had completed its regional certification process), with the potential to bring discredit to, and reduction of confidence in, the industry (Clause 2).

Janssen recognised the serious nature of these breaches and had already liaised with European colleagues to ensure that the above campaign had ceased and that no further activities relating to it were deployed. This was confirmed in writing by the third party provider.

Furthermore, Janssen was completing a local review of communications relating to this activity and had begun a dialogue with the senior European Stelara leadership team to identify what lessons could be learned and changes made following this specific incident.

Janssen concluded that the Crohn's Disease awareness campaign initiated by the European marketing team, but distributed to UK health professionals, amounted to pre-licence promotion. It was taking immediate steps to ensure that this could not be repeated. Janssen stressed that it was outside the usual process for the regional European team to initiate a campaign to UK clinicians without the prior approval of the UK team.

Given the nature and content of the material, Janssen was of the view that it had breached Clauses 3.2 (promotion outside the marketing authorization), 9.1 (failure to maintain high standards), 14.1 (failure to secure local certification) and that consideration should be given as to whether this may amount to a breach of Clause 2.

RESPONSE

Janssen provided a copy of the email (15 August) in which the UK marketing team was notified by the European team that the disease awareness campaign had been deployed and that it included UK gastroenterologists.

Janssen was unfortunately unable to provide electronic copies of the images available to Gastroenterology members accessing the Medscape website; the alerts appeared adjacent to other news headlines at that time. Customers clicking on the news headline were taken to the same email content 'Remission: Mapping new pathways for Crohn's disease treatment'. During that period, the headline 'Remission: the goal for all patients with Crohn's disease' followed by 'information from industry' were shown in three forms, desktop, news section and home page versions, to UK gastroenterologists.

According to the Janssen EMEA standard operating procedure (SOP), any European generated material had to be approved for use in local operating companies. A copy of the relevant SOP was provided.

Janssen UK submitted that the SOP was clear with regard to its scope and requirement for EMEA generated content to be sent to the countries for review and approval. Unfortunately, on this occasion that step was missed, due to human error. To avoid a repeat of this mistake the company would re-train all of its approvers on this SOP and re-emphasise specifically the need for local country approval in UNITAS (powered by Zinc) the electronic approval system for all such materials.

Janssen-Cilag submitted that although the Crohn's Disease awareness campaign initiated by the Janssen European team, but distributed to UK health professionals, was intended to be a disease awareness campaign, due to the inclusion of the links to information on Stelara (ustekinumab) this campaign qualified as pre-licence promotion; Stelara did not yet have a licensed indication for the treatment of Crohn's disease. This email campaign was a one-time event, it had ceased and no further activities relating to the campaign were being deployed.

Janssen recognised that the inclusion of links in the disease awareness campaign referring to product related information was not in line with the provided guidance on which the organisation was trained. This should not have happened and was certainly not the way Janssen wanted to do business.

Given the nature and content of the material, Janssen was of the view that it had breached Clauses 3.2 (promotion outside the marketing authorization), 9.1 (failure to maintain high standards) and 14.1 (failure to secure local certification). Janssen recognised that promotion outside of the marketing

authorisation was a particularly serious offence with the potential to bring discredit to, and reduction of confidence in the industry and therefore believed that consideration should be given as to whether this might also amount to a breach of Clause 2.

Janssen submitted that it took its responsibilities under the Code very seriously and deeply regretted this unfortunate error. It was completing an assessment of all activities leading up to this incident and also taking steps to identifying what lessons could be learned and changes made to avoid this situation in the future.

PANEL RULING

The Panel noted that the Code permitted certain activities prior to the grant of the marketing authorization. The supplementary information to Clause 3, Marketing Authorisation, stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited providing that any such information or activity did not constitute promotion prohibited by Clause 3 or any other clause. Clause 3.2 required that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC.

In the Panel's view it was not necessarily unacceptable for companies to conduct a disease awareness campaign and to use materials with health professionals that generated discussion prior to the grant of a relevant marketing authorization. The arrangements had to comply with the Code, particularly the requirements of Clause 3.

The Panel noted the Janssen in Europe had emailed UK health professionals without the involvement of Janssen UK which had therefore not certified the materials. This was not in line with the relevant SOP which, *inter alia*, required local approval of materials. The email could also be accessed from advertisements which read 'Remission: the goal for all patients with Crohn's disease. Information from industry'. These advertisements were accessible to members of Medscape who were gastroenterologists. Janssen submitted that these advertisements were seen by 1,042 UK gastroenterologists, 345 of whom accessed the email content.

The Panel was extremely concerned that advertisements and an email had been created and sent to UK health professionals by Janssen Europe without local approval of the materials. The supplementary information to Clause 1.11 Applicability of Codes required that activities carried out and material used by a pharmaceutical company located in a European country must comply with the national code of the European country as well as the national code of the country in which the activities took place or the materials were used. The Panel therefore considered that the advertisements and email came within the scope of the Code. Janssen UK was thus responsible for the use of the material in the UK.

The Panel noted that there appeared to be a serious error in that the relevant Janssen EMEA SOP required materials to be sent to the local company for approval prior to use and this had not happened. Janssen UK submitted that this was due to human error. This appeared to the Panel to be conduct that fell short of competent care.

The Panel examined the email in detail and considered that it was clearly promotional. It discussed the treatment of disease pathways of Crohn's disease and provided links to results of studies using Stelara for Crohn's Disease. It mentioned that Janssen was committed to discovering pioneering treatments for Crohn's disease and the need for more effective treatment options. Stelara was not indicated for Crohn's Disease. The advertisements were linked to the email and thus were also promotional. The Panel ruled a breach of Clause 3.2 of the Code as the material was inconsistent with the Stelara SPC as acknowledged by Janssen UK. The material had not been certified and a breach of Clause 14.1 was ruled as acknowledged by Janssen.

The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled as acknowledged by Janssen UK. It considered that by promoting an unlicensed indication and failing to certify the material it brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

During its consideration of this case the Panel was also concerned that the material might be disguised and thus might not meet the requirements of Clauses 12.1. It appeared from the heading to the email that the material was somewhat removed from Janssen. The very first piece of information being 'a communication from [named third party]'. The Panel queried whether this was so given that Janssen had in effect paid for the email. This misleading impression was reinforced by the heading 'Developed under the direction and sponsorship of Janssen Pharmaceutical Companies'. The Panel was also concerned that the email gave the impression that the new medicine from Janssen would provide 'the right treatment for the right person in every part of the world'. The claim in the advertisements 'Remission: the goal for all patients with Crohn's disease' might give the impression that the new product provided remission for all patients with Crohn's disease. These could be considered all-embracing and contrary to the requirements of Clause 7.10. The Panel requested that its concerns were drawn to Janssen's attention.

Complaint received **22 August 2016**

Case completed **6 October 2016**