CASE AUTH/2415/6/11

DIRECTOR v BIOGEN IDEC

Tysabri DVD

Leo Pharma advised the Authority that a Tysabri (natalizumab) DVD produced and distributed by Biogen Idec to health professionals and patients included a film clip demonstrating Leo's product Xamiol Gel (calcipotriol/betamethasone) on psoriasis (Case AUTH/2413/6/11). It thus appeared that Xamiol Gel, a prescription only medicine, might have been advertised to the public. In accordance with the Authority's Constitution and Procedure this matter was taken up with Biogen Idec as as a complaint under the Code.

The detailed response from Biogen Idec is given below.

The Panel noted that due to human error on a production run at a third party DVD manufacturer, promotional material for Xamiol had been placed on a DVD provided to patients who had been prescribed Tysabri.

A prescription only medicine had thus been promoted to the public, and the Panel ruled that Biogen Idec was in breach of the Code.

The Panel noted that Biogen Idec had certified the DVD in question in August 2010. Biogen Idec had engaged a different company to manufacture the DVD in 2011. The Panel noted that the manufacturing process involved uploading the approved electronic file on to the DVD; a process which was open to human error. The Panel noted the risk of human error and the serious consequences if such risk materialized in relation to material directed at patients. The Panel considered it would have been good practice for Biogen Idec, prior to distribution, to have checked a DVD from the production run against that certified by the company.

The Panel considered that the quality checks that Biogen Idec put in place as a result of this complaint should have been in place from the outset. These checks were particularly important when the material produced was intended for patients. High standards had not been maintained, and a breach of the Code was ruled.

The Panel did not consider that the circumstances brought discredit upon or reduced confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

The Director received information from which it appeared that Biogen Idec Limited might have contravened the Code. Paragraph 5.1 of the Constitution and Procedure for the Authority required that such a matter was taken up as a formal complaint under the Code.

COMPLAINT

Leo Pharma advised the Authority that a Tysabri (natalizumab) DVD produced and distributed by Biogen Idec to health professionals and patients included a film clip demonstrating Leo's product Xamiol Gel (calcipotriol/betamethasone) on psoriasis (Case AUTH/2413/6/11). It thus appeared that Xamiol Gel, a prescription only medicine might have been advertised to the public.

Biogen Idec was asked to respond in relation to Clauses 22.1, 9.1 and 2 of the Code.

RESPONSE

Biogen Idec confirmed that it had no conflicts of interest in this matter. Leo and Biogen Idec UK operated in different therapeutic areas (dermatology and neurology respectively), and were not competitors.

On Thursday, 9 June 2011, a Biogen Idec representative noted that a Tysabri DVD entitled 'A guide to MS [multiple sclerosis] and how Tysabri works' (TY-PAN-0177c April 2010) contained a 54 second video demonstrating the application of Leo's Xamiol Gel. The representative immediately notified Biogen Idec and returned the DVD. There was no narrative to accompany the video. The DVD was packaged in a DVD case (TY-PAN-0177d). No Tysabri material was present on the copy of the erroneous DVD.

The Tysabri DVD was intended to be provided to patients who had already been prescribed Tysabri by their health professionals. It contained factual information regarding Tysabri, multiple sclerosis, the infusion method for delivery, potential side effects, patient experiences and sources of further information.

The DVD was initially reviewed and certified in November 2008 via hard copy job bag (TY-PAN-23515 DVD). The Tysabri DVD was created and manufactured by an agency on behalf of Biogen Idec. The job bag was subsequently archived.

The Tysabri DVD was initiated for a re-review in April 2010, and reviewed/certified in August 2010 (TY-PAN-0177c) to incorporate updated product safety information. The DVD was provided to health professionals by representatives after 24 August 2010.

During the first quarter of 2011, production of the DVD and case was transferred to a new manufacturing vendor. This agency sub-contracted manufacture of the DVD disk. Both the current agency and the sub-contracted manufacturer were ISO9001 accredited. The content of the DVD was intended to be unchanged from the approved version, and no instruction was provided for the manufacturer to alter content.

The erroneous DVD in question related to the first and only production run of 1,015 DVDs manufactured by the sub-contracted agency. The DVDs were shipped from the manufacturer to the warehouse on 10 March 2011, and thence to representatives from 14 March 2011 onwards. Of the 1,015 DVDs, 738 remained in the warehouse. To date, Biogen Idec had not been notified of any other erroneous copies of this DVD. Once the error was detected on 9 June, a product recall process was immediately put in place to start the recall of all DVDs from all representatives and their return to the warehouse for destruction. All DVDs were dispatched to the warehouse for destruction by Monday 13 June (together with the remaining warehouse stock of 738 DVDs which were retained for destruction).

The previous and the current agency were contacted on 13 June and asked to conduct an internal investigation to determine how the error had occurred. A teleconference was held with both agencies on Wednesday 15 June to share feedback from the investigation. It was suspected that due to human error at the sub-contracted manufacturer the incorrect Xamiol file had been uploaded onto the Tysabri DVD. To date, Biogen Idec had not been notified of any erroneous copies of this DVD in the field other than the single copy notified by a representative on 9 June. The company was informed by the manufacturer that the error might not be universally apparent. This might explain why it had not been informed of further erroneous DVDs from patients or health professionals, nevertheless Biogen Idec took the precaution of recalling all relevant materials. It was possible that the mistake was an isolated case although this could not be verified by the manufacturer.

Leo was contacted on Wednesday 15 June to inform it of the incident, and Biogen Idec's actions to date. A further summary of actions was provided to Leo on 17 June. A copy of the affected DVD was couriered to Leo on the same day. Further calls were held with Leo during the following week.

On Monday 20 June a briefing document was sent to all UK representatives asking them to contact each clinic which might have been given copies of the DVD and collect any that the clinic had in stock for destruction (irrespective of DVD content). Clinics were informed that any DVD returned by patients due to having non-Tysabri content would be collected from the clinic and returned for destruction.

A face-to-face meeting was held with the current agency on Monday, 20 June. In addition to quality control steps which were in place at the manufacturer, further agreed, specific and documented quality control steps had been put in place for all electronic media manufactured by the current agency for Biogen Idec.

Although this was an unfortunate event, Biogen Idec strongly believed that this matter was out of its control. Biogen Idec submitted that it had acted promptly, diligently and with due care and consideration regarding the matter. The Tysabri material was reviewed and certified in accordance with the Code prior to release for manufacture. It had liaised closely with the current agency and Leo in a pro-active manner in an effort to implement quality control steps which exceeded requirements specified in the Code regarding review and approval of promotional and non-promotional materials. Biogen Idec did not believe it was in breach of Clauses 22.1, 9.1 or 2. It had maintained high standards in relation to the prompt withdrawal of materials, communication to the sales teams and Leo following the first detection of the production error.

In response to a request from the case preparation manager for further information Biogen Idec confirmed that the items returned by the representative were a DVD and a DVD case. The DVD case in question was correctly identified with Biogen Idec and Tysabri branding. The artwork on the returned DVD itself also was identifiable with the Biogen Idec and Tysabri logo, identified by item number, date of preparation, entitled 'A guide to MS and how Tysabri works', and supplemented by the clear statement 'For use only by patients who have been prescribed TYSABRI. Provided as a service to medicine by Biogen Idec Ltd'. However, the content contained Xamiol material only. No Tysabri information was present.

The information Biogen Idec sent to the Authority was a direct copy of all of the electronic content available on the single affected DVD the company had in its possession. Copies of exactly the same disks were sent to Leo on 17 June. For Leo's reference only, Biogen Idec labelled the disk 'Xamiol Patient Material for Leo'.

The DVD and DVD case provided to the sales force were not mislabelled. The representative played the content on the DVD, noticed that the DVD played Xamiol material, and promptly notified Biogen Idec.

The DVD was played prior to final certification in 2008. The certification process at that time involved hard copy review of transcripts and visual material, followed by review of the electronic media. A certification sticker corresponding to the item number was applied to the DVD cover.

Copies were provided of the final certification relating to the original Tysabri DVD content (TY00-PAN-23515, August 2008) and the re-certification of

the DVD and addition of further safety information (TY-PAN-0177c, August 2010). The item returned by the representative was visually identified and corresponded to these certified items, with the exception that the content of the DVD did not correlate with the content of the certified item. It solely contained the Xamiol information which was provided to Leo on 17 June. In addition a copy of the final certification of the updated DVD case artwork and design (TY-PAN-0177d, August 2010) was also provided to the Authority. A copy of the Tysabri DVD in its correct form, as certified, was provided.

As previously stated, the error occurred post-certification, during product manufacture. Although Biogen Idec fully appreciated and understood the concerns expressed by Leo, it considered that it had made all practicable efforts to support the company over the past weeks.

In response to a request from the Panel for further information, Biogen Idec confirmed that the DVD content was examined prior to final certification on 20 August 2010, as stated on the certificate. Biogen Idec stated that it was not possible to retain a physical copy of the item with the electronic job bag, however the copy of the actual DVD provided by the previous agency for signatory review and certification was filed and retained by the affiliate. A copy was provided. This was not a production copy, therefore was unmarked and unbranded. Production copies of the DVD were manufactured post-certification and provided to the sales force from August 2010.

Biogen Idec clarified that the erroneous DVD in question did not relate to material produced by the previous agency following certification of the material. Material from the previous agency production run was provided post-certification to health professionals during 2010, and utilised for 'in house' training during this time. No errors were observed by Biogen Idec or reported from the field from the previous agency production run. The erroneous DVD in question related to the production run from the current agency during the first quarter of 2011, following transfer of Tysabri DVD manufacture from the previous to the current agency. There were no changes to content. The material was not examined again or re-certified, given that it had not changed. The item number remained the same.

Biogen Idec outlined that the quality control measures in place during the manufacturing period were as follows:

- ISO9001 quality standards were in place at the current agency and the sub-contracted manufacturer. Quality Control (QC) checks were implemented in accordance with internal production protocols. The identity of the operator responsible for the production process was recorded on the QC record (initials or signature of the checker and counter (double) checker were recorded).
- Human error relating to inadvertent uploading of Xamiol material onto the Tysabri production DVD was noted following an investigation by the current agency.

To further enhance quality and mitigate risk of inadvertent error, the following additional quality control steps were agreed and put in place on 20 June 2011 for reproduction/resupply of the DVD following a face-to-face meeting with the current agency:

a) The agency would take a screen grab of the names of folders on the final proof copy of the DVD, and check vs the same information provided by Biogen Idec's creative agency prior to manufacture.

b) Total file size would be checked vs material received from the creative agency.

c) Last date modified (date and time record) would be checked vs material received from the creative agency.

Details would be captured on a proof approval form, which would be sent (along with final proof) to Biogen Idec. Final proof content would be checked at Biogen Idec, and the signed form would be returned to the agency (copy of which would be uploaded onto the relevant job bag internally). Three copies from the full production run would also be sent to Biogen Idec for checking.

Following a request from the Panel for clarification of the comment made by the manufacturer that 'the error might not be universally apparent', Biogen Idec explained that it had been informed of one erroneous Tysabri DVD. During the course of the investigation, the current agency stated that the presence of Leo material on its DVD might not be apparent upon viewing for every DVD it produced due to difference between hardware operating systems. Biogen Idec acknowledged that it did not fully understand how this could be so. As stated previously, whether or not this was an isolated case could not be verified by the manufacturer, therefore Biogen Idec decided to destroy remaining stock from the production run (738 out of 1,015 DVDs) regardless of content, and recall remaining Tysabri DVDs held by its representatives and within clinics. Biogen Idec considered that taking prompt action based on the assumption that all DVDs from the current agency production run might have been affected was more appropriate than initiating an investigation to determine the number of DVDs affected and subsequently initiating a selective recall.

PANEL RULING

The Panel noted that Clause 22.1 prohibited the promotion of a prescription only medicine to the public. The Panel noted that promotional material for Leo's product Xamiol had been placed on a DVD provided to patients who had been prescribed

Tysabri. According to Biogen Idec this had occurred due to human error on a production run at a third party DVD manufacturer some months after the DVD was certified. The Panel did not accept Biogen Idec's submission that this matter was out of its control. It was a well established principle that a company was responsible for the acts or omissions of its agents or third parties. If this were not the case companies would be able to rely on such acts or omissions to circumvent the requirements of the Code. Biogen Idec was responsible for the acts or omissions of the DVD manufacturer.

The Panel noted that a DVD distributed to patients contained a video clip for a prescription only medicine. A prescription only medicine had thus been promoted to the public, and the Panel ruled a breach of Clause 22.1.

The Panel noted that Biogen Idec had certified the DVD in question on 20 August 2010 and copies were provided to the sales force for distribution after 24 August 2010. Biogen Idec had engaged a new company to manufacture the DVD in the first quarter of 2011. The Panel noted that the manufacturing process involved uploading the approved electronic file on to the DVD; a process which was open to human error. The Panel noted the risk of human error and the serious consequences if such risk materialized in relation to material directed at patients. The Panel considered it would have been good practice for Biogen Idec, prior to distribution, to have checked a DVD from the production run against that certified by the company. This was especially so given it was working with a new manufacturer.

The Panel was concerned that the error was discovered not by process checks at head office, but by a representative in the field. The Panel considered that the quality checks that Biogen Idec put in place as a result of this complaint should have been in place from the outset. These checks were particularly important when the material produced was intended for patients. High standards had not been maintained, and a breach of Clause 9.1 was ruled.

The Panel noted that the DVD in question appeared to have been certified in accordance with the Code. It was unfortunate that Biogen Idec had been let down by its DVD manufacturer. Nonetheless, a prescription only medicine had been advertised to the public. The Panel noted its comment above about the quality checks now in place at Biogen Idec. The Panel noted its rulings of breaches of the Code above and considered, on balance, that the circumstances did not warrant additional censure. A ruling of a breach of Clause 2 was a sign of particular censure, and was reserved for such circumstances. The Panel did not consider on balance that the circumstances brought discredit upon or reduced confidence in the industry, and ruled no breach of Clause 2.

Proceedings commenced	**27 June 2011**
Case completed	**4 August 2011**