CASES AUTH/3359/6/20 and AUTH/3360/6/20

NHS EMPLOYEE v GLENMARK and iQ PHARMA

Promotion of Renocontin

An anonymous, non-contactable, NHS employee complained about the promotion of Renocontin (prolonged release oxycodone hydrochloride). The material (ref PP-UK-REN-0002) was issued by CactusRx which was a trading style of iQ Pharma Limited. iQ Pharma distributed Renocontin under licence from Glenmark Pharmaceuticals Limited which was the marketing authorization holder. The material stated that prescribing Renocontin by brand could halve prescribing costs for prolonged release oxycodone hydrochloride tablets. A cost comparison table compared the cost of various presentations of Renocontin (from 5mg to 80mg) with the cost of competitor products. Renocontin was indicated for severe pain which could only be managed with opioids.

The complainant explained that he/she was reviewing opioids within his/her practice; the material at issue had been received from a colleague. The complainant alleged that the information was misleading as it implied that a Renocontin 80mg tablet was available which was not so - only the 5 to 60mg strengths were. The 80mg tablet was also referred to in a claim on bioequivalence vs OxyContin. The complainant also noted that the summary of product characteristics (SPC) was updated in March 2019 but that the prescribing information included in the material had been prepared in January 2019.

The detailed responses from Glenmark and iQ Pharma are given below.

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The Panel noted that Renocontin tablets were available in seven different strengths from 5mg to 60mg. Although a marketing authorization for an 80mg tablet had been granted, that presentation had not been made commercially available. The cost comparison table within the material provided by the complainant was arranged in a number of columns. The left-hand column was headed 'Presentation' and listed below were 5mg,10mg, 15mg, 20mg, 30mg, 40mg, 60mg and 80mg* presentations of prolonged release oxycodone tablets; the asterisk led the reader to a footnote which read 'as 2 x 40mg'. The columns to the right were labelled with the various brands of prolonged release oxycodone available including 'iQ Pharma Renocontin'. Given the construction of the table, the Panel disagreed with the implied submission that the footnote 'as 2 x 40mg' only applied to Renocontin, as written, the footnote applied to all of the medicines listed to the right despite the fact that all of those listed, other than Renocontin, were available as 80mg. Given the availability of 80mg tablets for other brands of prolonged release oxycodone, and the familiarity that prescribers might have with using those tablets, the Panel considered that the cost comparison table was misleading as it implied that an 80mg tablet of Renocontin was also available; in the Panel's view, the footnote was not sufficient to negate the misleading impression. Although an 80mg dose of Renocontin could be prescribed, a health professional should know, from the outset, that unlike the

competitors listed, a prescription for that dose could only be achieved with the concomitant use of at least two tablets which, in itself, might have an adverse impact on patient compliance vs the use of one 80mg tablet. Patients who were used to taking an 80mg dose with just one tablet might be confused if a repeat prescription was filled with Renocontin. The material referred to the cost savings if GP practices switched from Longtec/Abtard to Renocontin. The Panel considered that the cost comparison table was misleading and a breach of the Code was ruled.

The Panel noted its comments above and similarly considered that the claim 'Bioequivalence to OxyContin tablets in strengths 5mg, 20mg, 40mg and 80mg in steady state has been proven' was misleading. Although a statement of fact, it implied that, as with Oxycontin, there was an 80mg tablet of Renocontin available which was not so. A breach of the Code was ruled.

With regard to the prescribing information, the Panel noted that the Renocontin SPC had been updated in June 2019 to include a precaution about the concomitant use of serotonin agents.

The Panel noted Glenmark's submission that it had identified clear communication internally between the regulatory and commercial functions notifying an update to the Renocontin SPC, however, this message appeared not to have been forwarded to the external commercialisation partner for Renocontin. The Panel noted that the prescribing information on the material provided by the complainant was dated January 2019; the complainant had received a copy of the material from a colleague, not from Glenmark. The complainant was non-contactable and so could not be asked for details as to when both he/she and his/her colleague had first received the material. Nonetheless, it appeared from Glenmark's submission that the material, which should have been updated in June 2019, was not withdrawn until the company drew up corrective and preventative actions in response to this complaint almost a year later (May 2020). The Panel noted Glenmark's admission that 23 copies of the material had been used without the update in July 2019. It was possible that the complainant's colleague had received one of those copies which thus did not contain a succinct statement of all of the precautions likely to be needed in the prescribing of Renocontin. In the Panel's view, prescribing information was an important component of patient safety. A breach of the Code was ruled.

The Panel noted its comments and rulings above and was extremely concerned that patient compliance and patient safety might have been compromised. A breach of the Code was ruled.

Case AUTH/3360/6/20

The Panel's rulings in this case were the same as for Case AUTH/3359/6/20 above.

An anonymous, non-contactable, NHS employee complained about promotional information for Renocontin (prolonged release oxycodone hydrochloride) (ref PP-UK-REN-0002). The material was issued by CactusRx which was a trading style of iQ Pharma Limited. iQ Pharma distributed Renocontin under licence from Glenmark Pharmaceuticals Limited which was the marketing authorization holder. It was stated in the material that prescribing Renocontin by brand could half prescribing costs for prolonged release oxycodone hydrochloride tablets. A cost

comparison table compared the cost of various presentations of Renocontin (from 5mg to 80mg) with the cost of competitor products. Renocontin was indicated for severe pain which could only be managed with opioids.

COMPLAINT

The complainant explained that he/she was undertaking a review of opioid products within his/her practice and the material at issue had been passed to him/her from a colleague. The complainant stated that he/she had found the information misleading as at first glance there appeared to be an 80mg tablet available as that strength was included within the table of presentations. There was also mention of an 80mg tablet included in a claim on bioequivalence vs OxyContin. On searching the electronic Medicines Compendium (eMC) for the 80mg tablet, the complainant noted that it was not listed – only the 5 to 60mg strengths. The complainant also noted that the summary of product characteristics (SPC) was updated in March 2019 but that the prescribing information included in the material at issue had been prepared in January 2019.

When writing to Glenmark Pharmaceuticals and iQ Pharma, the Authority asked it to consider the requirements of Clauses 4.1, 7.2 and 9.1 of the Code.

RESPONSE

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Glenmark explained that Renocontin was commercialised on its behalf by iQ Pharma Limited and its affiliates. Glenmark and iQ Pharma were independent companies and the relationship between them was an arm's length, commercial arrangement governed by a formal exclusive distribution agreement. Aside from commercial aspects, this agreement addressed compliance related matters and clearly defined the respective parties' responsibilities including, but not limited to, ensuring adequate and timely performance of pharmacovigilance activities and recall procedures as well as the promotion of Renocontin. Glenmark stated that, as marketing authorization holder for Renocontin, it was also responsible for ensuring a compliant approach to the commercialisation of the medicine.

Glenmark acknowledged that the material at issue included a table which allowed readers to compare the acquisition costs of the available presentations of Renocontin. Although an 80mg presentation had not been commercialised, Glenmark, nevertheless, held a corresponding UK marketing authorization. In light of this, Glenmark considered that the table represented an accurate and fair cost comparison across the available brands and the reference to the price of the 80mg presentation being comprised of 2x40mg tablets of Renocontin was both necessary and clearly denoted immediately below. Glenmark considered that this was the most accurate representation of how a prescription for the 80mg presentation of Renocontin would reasonably (and lawfully) be dispensed with the currently available presentations.

In terms of bioequivalence, the material included the claim 'Bioequivalence to OxyContin tablets in strengths 5mg, 20mg, 40mg and 80mg has been proven'. This was a statement of fact and reflected the cited publication (copy provided). The claim reflected the conclusions of the formal regulatory assessment of Renocontin by the Medicines and Healthcare products Regulatory Agency (MHRA) which formed the basis of the marketing authorization approvals for the 5mg, 10mg, 15mg, 20mg, 30mg, 40mg, 60mg and 80mg presentations of Renocontin. Given the

pricing statements made earlier in the material, stating the precise bioequivalence that had been demonstrated to the innovator product (Oxycontin), this was a reasonable claim and relevant comparison.

Glenmark stated that the promotional material was approved in line with relevant Glenmark standard operating procedures (SOPs) and submitted for review and approval in line with pharmaceutical industry practices. Glenmark used an online approval platform and the certificate of approval for the material in question was provided on 11 February 2019. Glenmark provided a copy of the final material with certification and the references cited therein along with details of its final signatory.

Following approval, the materials were first distributed by iQ Pharma's affiliate on 14 February 2019. A Type IB variation to the Renocontin SPC was submitted by Glenmark on 26 March 2019 and this was subsequently approved by the German regulatory authority on 5 June 2019. Copies of both the original and updated SPCs as well as this approval were provided.

Glenmark stated that irrespective of whether March 2019 or June 2019 was the relevant date for the purposes of establishing implementation of a Type 1B variation, following investigative discussions with iQ Pharma, it transpired that limited distribution (23 copies) of the promotional item in question took place in July 2019. In either scenario, the promotional item was circulated following the update to the corresponding SPC and, in this respect, Glenmark recognised that the materials should have been updated to reflect the new SPC. The failure to withdraw, amend and recertify the materials accordingly reflected a failure to adhere to the requirements imposed in this regard.

Glenmark stated that although there were various SOPs in place designed to prevent such a situation from arising, not least the requirement for the regulatory team to timely notify the commercial team of any updates to product SPCs, these had not operated effectively in this instance. Glenmark submitted that this was due to the nature of the commercialisation arrangement whereby the promotional item was produced and circulated by a third party, iQ Pharma and its affiliates, and who were the only Glenmark partner with whom such practice was adopted. Indeed, Glenmark had identified clear communication internally between the regulatory and commercial functions notifying an update to the Renocontin SPC (copy provided), however, due in part to significant levels of attrition within Glenmark's marketing function, this message appeared not to have been forwarded to the external commercialisation partner for Renocontin. In support of this claim, Glenmark stated that all other products for which Glenmark held the marketing authorization, and which were commercialised 'in-house', did not have version inconsistencies between their corresponding SPCs and prescribing information.

Glenmark stated that, nevertheless, it recognised the deficiency in its process in this instance and had opened a corrective and preventative actions (CAPA) in a bid to ensure that such errors did not occur in future. This included immediate withdrawal of the promotional item and the updating and creation where necessary of SOPs to adequately address the commercialisation of products promoted by third parties. Furthermore, Glenmark had appointed a regulatory training manager who would be responsible for ensuring appropriate communication across the relevant functions. Glenmark confirmed that there had been no other promotional items produced for Renocontin.

Glenmark submitted that when it was certified the material at issue contained prescribing information consistent with the SPC. Glenmark acknowledged that when the SPC was updated, the prescribing should have been updated and the material withdrawn. The CAPA addressed this error and, as outlined above, a number of actions were being undertaken to prevent this from recurring.

As described above, Glenmark considered that the material at issue contained accurate, balanced, fair, objective and unambiguous claims and comparisons. The item was based on an up-to-date evaluation of all the evidence and reflected that evidence clearly. Representation of the cost comparisons was clear, fair and accurate. The statement regarding bioequivalence was accurate and reflected the available evidence. Neither claim was misleading.

Glenmark stated that it worked hard to achieve and maintain high standards at all times. The company accepted that, on this occasion, there had been a failing in its process to ensure that the change to the SPC triggered an update to the promotional item. The opened CAPA, as described above, addressed the required internal actions.

RESPONSE

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iQ Pharma noted that the material at issue included an illustrated table which allowed readers to compare the NHS costs of the available presentations of prolonged release oxycodone. Neither Glenmark nor iQ Pharma had commercialised the 80mg presentation of Renocontin although Glenmark held the relevant UK marketing authorization. In light of that, iQ Pharma considered that the table represented an accurate and fair cost comparison across the available brands and the reference that the price of the 80mg presentation of Renocontin was comprised of 2x40mg tablets was both necessary and clearly denoted immediately below.

iQ Pharma submitted that the claim that 'Bioequivalence to OxyContin tablets in strengths 5mg, 20mg, 40mg and 80mg has been proven' was a statement of fact and reflected the cited publication. The claim reflected the conclusions of the formal regulatory assessment of Renocontin by the Medicines and Healthcare products Regulatory Agency (MHRA) which formed the basis of the marketing authorization approvals for the 5mg, 10mg, 15mg, 20mg, 30mg, 40mg, 60mg and 80mg tablets. Given the pricing statements made earlier in the material, stating the precise bioequivalence that had been demonstrated to the innovator product (Oxycontin), this too was a reasonable claim and relevant comparison.

iQ Pharma stated that the material was approved in line with its internal system and standard operating procedures (SOPs) for the approval of marketing materials. The material was also reviewed and approved in conjunction with Glenmark which used an electronic approval platform. All materials were approved and the certificate of approval for the material was provided on 11 February 2019.

iQ Pharma recognised the need under Clause 14.1 (Joint Ventures and Co-Promotion) to have its own internal approval process but to ensure the company's activities did not cause issues for Glenmark, iQ Pharma had agreed to submit any and all materials for its own review and approval. Only then would iQ Pharma use a promotional piece.

Following approval, the materials were first distributed in February 2019. From iQ Pharma's internal review and in discussion with Glenmark, iQ Pharma now noted that a Type IB variation to the Renocontin summary of product characteristics (SPC) was submitted by Glenmark in March 2019 and subsequently approved by the MHRA on 5 June 2019. The material in question was emailed to 23 healthcare decision makers in early July 2019. As the material was used after the SPC update, iQ Pharma recognised that it too should have been updated and the failure to withdraw, amend or update the piece was a failure on its part.

iQ Pharma stated that its internal review had revealed that, despite best endeavours, there was a deficiency in its processes, and the company should have sought to regularly review the validity of the SPC being used in this piece. Subsequently, iQ Pharma had opened a CAPA and amended its SOPs to ensure it proactively sought updates from its partner organisations, so it could prevent such events happening again.

4.1 Prescribing information

iQ Pharma stated that when it was certified the material contained prescribing information which was consistent with the SPC. iQ Pharma acknowledged that when the SPC was updated, the prescribing information should have been updated and the promotional piece withdrawn. iQ Pharma believed the CAPA addressed that error with corrective actions being put in place to prevent it from happening again.

7.2 Information, claims and comparisons

iQ Pharma believed that the promotional information contained accurate, balanced, fair, objective and unambiguous claims and comparisons. The material was based on an up-to-date evaluation of all the evidence and reflected that evidence clearly. Representation of the cost comparisons was clear, fair and accurate. The statement regarding bioequivalence was accurate and reflected the available evidence. iQ Pharma submitted that neither claim was misleading.

9.1 High standards

iQ Pharma submitted that it worked hard to achieve and maintain high standards across all aspects of the business from the promotion, storage and distribution of medicines.

iQ Pharma stated that all personnel involved in the production of materials and promotion of products had taken the ABPI examination with former employers and whilst the company was not a member of the ABPI, it continued to hold those standards in its business practices, annually reviewing the principles of the Code as part of ongoing training.

iQ Pharma stated that it always strove to ensure the integrity of the Code for its partners, the company and the wider industry. The company accepted its processes had failed to ensure that the SPC change triggered an update to the promotional item. The CAPA, described above, addressed the required internal actions it had adopted, and it was working with Glenmark to ensure that this did not happen again.

PANEL RULING

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The Panel noted that Renocontin tablets were available in seven different strengths from 5mg to 60mg. Although a marketing authorization for an 80mg tablet had been granted, that presentation had not been made commercially available. The cost comparison table within the material provided by the complainant was arranged in a number of columns. The left-hand column was headed 'Presentation' and listed below were 5mg,10mg, 15mg, 20mg, 30mg, 40mg, 60mg and 80mg* presentations of prolonged release oxycodone tablets; the asterisk led the reader to a footnote which read 'as 2 x 40mg'. The columns to the right were labelled 'iQ Pharma Renocontin', 'Cost Relative to Longtec', 'Qdem, Longtec', 'Napp Oxycontin', 'Ethypharm, Abtard' and 'Wockhardt, Oxeltra'. Given the construction of the table, the Panel disagreed with the implied submission that the footnote 'as 2 x 40mg' only applied to Renocontin. The footnote, as written, applied to all of the medicines listed to the right despite the fact that all of those listed, other than Renocontin, were available as 80mg. Given the availability of 80mg tablets for other brands of prolonged release oxycodone, and the familiarity that prescribers might have with using those tablets, the Panel considered that the cost comparison table was misleading as it implied that an 80mg tablet of Renocontin was also available; in the Panel's view, the footnote was not sufficient to negate the misleading impression. Although an 80mg dose of Renocontin could be prescribed, a health professional should know, from the outset, that unlike the competitors listed, a prescription for that dose could only be achieved with the concomitant use of at least two tablets which, in itself, might have an adverse impact on patient compliance vs the use of one 80mg tablet. Patients who were used to taking an 80mg dose with just one tablet might be confused if they got a repeat prescription filled with Renocontin and now needed to take two tablets. The material referred to the cost savings if GP practices switched from Longtec/Abtard to Renocontin. The Panel considered that the cost comparison table was misleading and a breach of Clause 7.2 was ruled.

The Panel noted its comments above and similarly considered that the claim 'Bioequivalence to OxyContin tablets in strengths 5mg, 20mg, 40mg and 80mg in steady state has been proven' was misleading. Although a statement of fact, it implied that, as with Oxycontin, there was an 80mg tablet of Renocontin available which was not so. A breach of Clause 7.2 was ruled.

With regard to the prescribing information, the Panel noted that the Renocontin SPC had been updated in June 2019 to include the following:

> 'Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.'

The Panel noted Glenmark's submission that it had identified clear communication internally between the regulatory and commercial functions notifying an update to the Renocontin SPC, however, this message appeared not to have been forwarded to the external commercialisation partner for Renocontin. The Panel noted that the prescribing information on the material provided by the complainant was dated January 2019. The Panel noted that the complainant had received a copy of the material from a colleague, not from Glenmark. The complainant was

non-contactable and so could not be asked for details as to when both he/she and his/her colleague had first received the material. Nonetheless, it appeared from Glenmark's submission that the material, which should have been updated in June 2019, was not withdrawn until the company drew up a CAPA in response to this complaint almost a year later (May 2020). The Panel noted Glenmark's admission that 23 copies of the material had been used without the update in July 2019. It was possible that the complainant's colleague had received one of those copies which thus did not contain a succinct statement of all of the precautions likely to be needed in the prescribing of Renocontin. In the Panel's view, prescribing information was an important component of patient safety. A breach of Clause 4.1 was ruled.

The Panel noted its comments and rulings above and was extremely concerned that patient compliance and patient safety might have been compromised. A breach of Clause 9.1 was ruled.

PANEL RULING

Case AUTH/3360/6/20

The Panel ruled two breaches of Clause 7.2 and breaches of Clauses 4.1 and 9.1 as in Case AUTH/3359/6/20 above.

Complaint received **3 June 2020**

Cases completed **30 November 2020**