CASE AUTH/2920/12/16

ANONYMOUS, NON-CONTACTABLE EX-REPRESENTATIVE v UCB

Promotion of Naloxone Minijet

An anonymous, non-contactable ex-representative of UCB Pharma alleged that he/she was asked to promote Naloxone Minijet Injection off licence.

The complainant explained that naloxone was a generic product and many other companies marketed it. UCB's naloxone had a narrow indication mainly for the treatment of respiratory depression induced by natural and synthetic opioids. The complainant submitted, however, that naloxone marketed by Martindale had a broader indication in that it was licensed for complete and partial reversal of opioid depression and not only the respiratory depression associated with it.

The complainant submitted that in 2012 the Advisory Council on the Misuse of Drugs recommended that take-home naloxone should be made more widely available. Public Health England also produced guidance on promoting the wider availability of naloxone to reduce overdose deaths from heroin and the like.

Under this guidance, naloxone could be supplied to anyone who: currently used illicit opiates such as heroin; received opioid substitution therapy; left prison with a history of drug use or previously used opiates (to protect in the event of relapse). Under this guidance, with the agreement of someone to whom naloxone could be supplied, it could also be provided to their family members, carers, peers and friends. Other UK nations also came up with similar guidelines.

The complainant stated that UCB representatives were asked to promote take-home naloxone Minijets to prescribers, pharmacists and budget holders. Representatives were told by their line manager that by doing this the sales of UCB's product would increase which would easily help to achieve targets. The complainant also referred to a poster which was produced for a company sales meeting by one of his/her colleagues in the Minijets team.

The complainant was concerned that although government agencies published clear guidelines on naloxone take-home, UCB's naloxone was not licensed for this indication but representatives were asked to actively promote it in this indication for financial gains. The company asked representatives to pursue a course of action which was in breach of the Code. The complainant alleged that the company and senior managers did not maintain high standards because the poster was presented and commended at a national sales conference and no one picked it up. There were also patient safety issues in keeping and properly administering an injectable as the complainant did not remember any training support for the same. The complainant alleged that UCB acted in a highly unprofessional way and that this activity was known to many senior managers and had happened for a long time; if unchecked these types of activities could bring discredit to the whole industry.

The complainant noted that UCB had recently sold the entire Minijets product portfolio to a third party but in his/her view a company could be reprimanded for its historical wrong doings.

The detailed response from UCB is given below.

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure stated that anonymous complaints would be accepted, but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant could not be contacted for more information. The Panel noted the parties' interpretation of the licensed indication for naloxone Minijet differed.

The Panel noted that naloxone Minijet 400mcg/ml was indicated for the treatment of respiratory depression induced by natural or synthetic opioids. The medicine was presented as prefilled syringes of 1 or 2mls (400 or 800mcg). The usual initial adult dose was 400 - 2000mcg every 2 to 3 minutes if necessary. If no response was observed after the administration of 10mg then the depressive condition might be caused by a medicine or a disease process not responsive to naloxone. Treatment of overdose might thus require the use of a number of Minijet syringes. Use of naloxone Minijet in the non-medical setting was not referred to in the SPC and in that regard it did not appear that the product was specifically intended or packaged for such use and so non-medical responders might find it more difficult to use than other forms of naloxone, particularly Martindale's Prenoxad. Nonetheless, the Panel did not consider that take-home use of naloxone Minijet was off licence *per se* as alleged. No breach of the Code was ruled.

The Panel disagreed with UCB's submission that the poster was not briefing material for the representatives; it had been presented at an internal UCB conference with the purpose of sharing best practice. The Panel assumed that as the poster had been developed by a representative, it mirrored what he/she considered was acceptable to claim about naloxone Minijet. The Panel noted that the poster did refer to training family friends, however it was extremely concerned that the title of the poster stated, without qualification, 'Minijet team Naloxone: How a Take Away Can Save

Hundreds of Lives'. There was no reference cited in support of the statement and no indication as to the time period over which hundreds of lives would be saved by naloxone Minijet. Additional text stated that an overdose could now be referred to in the present tense: 'I have a friend who [overdosed] last week. Naloxone did that' which implied that naloxone saved the lives of everyone who overdosed. The poster also stated that naloxone Minijet provided the ideal offering, and in that regard the Panel noted its comments above about Prenoxad. The poster also stated that naloxone Minijet had the potential to dominate the market and that the dose of the competitor was too high. The Panel considered that the content of the poster was such that it advocated claims for take-home naloxone Minijet, or the competitor, which were likely to be in breach of the Code. A breach of the Code was ruled. Overall the Panel considered that, given its content, the production of the poster showed poor judgement and in that regard it ruled a breach of the Code as it considered that high standards had not been maintained.

The Panel noted its rulings and comments above and although it had some concerns, it did not consider that the circumstances were such as to rule a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

A non-contactable, ex-representative complained about the promotion of Naloxone Minijet injection by UCB Pharma Ltd alleging that he/she was asked to promote the medicine off licence.

COMPLAINT

The complainant stated that he/she joined UCB relatively new to the industry and not very well versed on the Code. Since leaving the company and after working in the industry for a few years now, he/she had a much broader understanding of the Code. With his/her current knowledge, the complainant was horrified about what UCB asked its representatives to do and being a conscientious person, he/she was now complaining.

The complainant explained that he/she joined UCB as a representative in the mature products business unit which had a product range called IMS, consisting of several injectable products for emergency use. One of the products, naloxone, was indicated for:

> 'the treatment of respiratory depression induced by natural and synthetic opioids, such as codeine, diamorphine, levorphanol, methadone, morphine, concentrated opium alkaloid hydrochlorides and propoxyphene. It is also useful for the treatment of respiratory depression caused by opioid agonist/antagonists nalbuphine and pentazocine. Naloxone is also used for the diagnosis of suspected acute opioid overdose.' (emphasis added).

UCB's naloxone was indicated mainly for the treatment of respiratory depression induced by various agents. Naloxone, however, was a generic product and many other companies marketed it, including Martindale whose product was indicated for:

> 'the complete or partial reversal of opioid depression, including mild to severe respiratory depression induced by natural and synthetic opioids, including dextropropoxyphene, methadone and certain mixed agonist/antagonist analgesics: nalbuphine and pentazocine. It may also be used for the diagnosis of suspected acute opioid overdosage. Naloxone may also be used to counteract respiratory and other CNS depression in the new-born resulting from the administration of analgesics to the mother during childbirth.'(emphasis added).

The complainant submitted that the Martindale indication was broader than UCB's naloxone and was for complete and partial reversal of opioid depression and not only the respiratory depression associated with it, which was the narrow indication for UCB's naloxone.

Besides indications, there were other differences in the qualitative and quantitative composition of the various naloxones available in the market.

The complainant submitted that in 2012 the Advisory Council on the Misuse of Drugs recommended that take-home naloxone should be made more widely available. Public Health England also produced guidance for local authorities and local partners on promoting the wider availability of naloxone to reduce overdose deaths from heroin and the like.

Under this guidance, naloxone could be supplied to anyone who: currently used illicit opiates such as heroin; received opioid substitution therapy; left prison with a history of drug use or previously used opiates (to protect in the event of relapse).

Under this guidance, with the agreement of someone to whom naloxone could be supplied, it could also be provided to their family members, carers, peers and friends. Other UK nations also came up with similar guidelines.

The complainant stated that UCB representatives who promoted the Minijets Naloxone range were asked to promote take-home naloxone to prescribers, pharmacists and budget holders. Representatives were told by their line manager that by doing this the sales of UCB's product would increase and that take-home naloxone would easily help to achieve targets. This was mentioned at team meetings and via emails. The complainant also referred to a poster which was produced for a company sales meeting by one of his/her colleagues in the Minijets team; the poster was highly commended.

The complainant stated that his/her concerns were that although government agencies published clear guidelines on naloxone take-home, UCB's naloxone was not licensed for this indication but representatives were asked to actively promote it in this indication for financial gains, in breach of Clause 3. The company asked representatives to pursue a course of action which was in breach of Clause

15.9. The complainant alleged that the company and senior managers did not maintain high standards because the poster was presented and commended at a national sales conference and no one picked it up. There were also patient safety issues in keeping and properly administering an injectable as the complainant did not remember any training support for the same. The complainant alleged that UCB acted in a highly unprofessional way and that this activity was known to many senior managers and had happened for a long time; if unchecked these types of activities could bring discredit to the whole industry.

The complainant heard that recently UCB sold the entire Minijets product portfolio to a third party but in his/her view a company could be reprimanded for its historical wrong doings.

In writing to UCB, the Authority asked it to bear in mind Clauses 9.1 and 2 in addition to Clauses 3 and 15.9 as cited by the complainant.

RESPONSE

UCB noted that there was nothing specific in the complaint regarding the time period but the dating of the poster referred to by the complainant allowed it to assume early 2012.

Relevant chronology of events and licensed indications

UCB stated that naloxone was an opioid antagonist used to counteract opiate respiratory depression induced by natural and synthetic opioids. Naloxone Hydrochloride Minijet 400mcg/ml was commercialised by UCB as part of a portfolio of critical care sterile injectable products. As of June 2016, the complete Minijet portfolio was divested along with the company to International Medications System Ltd which was the registered marketing authorisation holder for the products.

The complainant referred to the indications from the summaries of product characteristics (SPCs) for two naloxone products, the UCB Minijet 400mcg/ml and the product licensed by Martindale Pharma (1mg/ml).

UCB stated that the naloxone Minijet was was first licensed in 1986 and since then had always been indicated for:

> 'the treatment of respiratory depression induced by natural and synthetic opioids, such as codeine, diamorphine, levorphanol, methadone, morphine, concentrated opium alkaloid hydrochlorides and propoxyphene. It is also useful for the treatment of respiratory depression caused by opioid agonist/antagonists nalbuphine and pentazocine. Naloxone is also used for the diagnosis of suspected acute opioid overdose'.

The Martindale naloxone, according to its SPC:

> 'may be used for the complete or partial reversal of opioid depression, including mild to severe respiratory depression induced by natural and synthetic opioids, including dextropropoxyphene, methadone and certain mixed agonist/antagonist analgesics: nalbuphine and pentazocine. It may also be used for the diagnosis of suspected acute opioid overdosage. Naloxone may also be used to counteract respiratory and other CNS depression in the new-born resulting from administration of analgesics to the mother during childbirth'.

The two products had different concentrations of naloxone but both were indicated for the treatment of respiratory depression induced by natural and synthetic opioids, and in essence the indications could be considered as having core similarities both in wording and clinical use.

Well before 2012, the take-home concept was well accepted and established in practice. In 2005, in light of the clear potential of naloxone to save life and the need for naloxone-based overdose prevention programmes, naloxone was added to the list of medicines that could be given parentally (intramuscularly, intravenously or subcutaneously) by any member of the public for the purpose of saving a life (Medicines and Healthcare products Regulatory Agency (MHRA) 2005). A prescription was still needed for the opiate user at risk but the medicine could then be kept for them by other people, like family members, partners or other carers, who could legally use it in an emergency.

From 2007 onwards, pilot take-home naloxone programmes aimed at preventing overdose-related deaths started at local and national level as clinically driven and evidence-based initiatives. Many important guidelines, like the 'Drug Misuse and Dependence: UK Guidelines on Clinical Management' supported this course of action. Naloxone Minijet was one of the choices of medicine available then for clinicians to use in such a setting, and was considered licensed for such use.

UCB noted that up until mid-2012, all naloxone products to be used in the take-home setting had to be re-packaged, often by the healthcare service, to be distributed through emergency kits. In June 2012, Martindale's Prenoxad (naloxone) was introduced, with use in the community setting specifically detailed. The product composition was the same as Martindale's naloxone hydrochloride injection 1mg/ml, with the addition of two suitable needles in order to minimize the need of any secondary re-packaging and the patient information leaflet was updated accordingly. The clinical indication of Prenoxad was the same as other naloxone products ('complete or partial reversal of respiratory depression induced by natural and synthetic opioids', from the Prenoxad SPC) with additional information regarding the use setting ('intended for emergency use in the home or other non-medical setting by appropriate individuals or in a health facility setting', from the Prenoxad SPC).

The addition of the needles and of a brand name differentiated the product from Martindale's existing naloxone injection, and enabled prescribers to select a package designed specifically for community use. However, the additional wording of the Prenoxad licence did not exclude other naloxone products from use in the community setting.

UCB stated that UK Medicines Information (UKMi), a well-established and reputed body that reviewed the practical use of products in relevant clinical settings, supported this concept in its recent document 'In use product safety assessment report: naloxone products for emergency opiate reversal in non-medical settings', March 2016. The review assessed the four UK licensed naloxone products available in a prefilled syringe, among which naloxone Minijet 400mcg/ml based on clinical experience since before 2012.

In particular, on page 2 under 'Licensing status' the review reported that 'All naloxone prefilled syringe products were licensed for the reversal/treatment of opioid induced respiratory depression. Prenoxad was specifically developed for use in community and as such the product licence specified it can be used in the home, non-medical setting or in a health facility setting … The product licences for the three non-proprietary products do not indicate use for a specific setting or user'. The review concluded on page 4 with two considerations on which product to choose to safely deliver naloxone dosing in a non-medical setting:

- It is vital that naloxone products supplied are suitable for the non-medical setting; in our view prefilled syringes are the preferred formulation choice compared to vials or ampoules.
- Each of the four prefilled syringe products are presented differently and thus features of each should be considered carefully […].'

For the reasons above, UCB submitted that naloxone Minijet had the same clinical indication in treating respiratory depression induced by natural and synthetic opioid as Martindale's products. The medicine treatment services choice of which product to use in a take-home setting, as suggested by the UKMi review, was based on many factors including, *inter alia*, dose, product packaging and facility of administration. Therefore, there was no out-of-licence promotion of naloxone Minijet.

Poster and alleged out-of-licence promotion

UCB provided a copy of the non-promotional poster, dated March 2012; it was for internal use only and was not a sales briefing on how to promote the product.

The poster was created by a key account manager in the Minijet team and highlighted the fact that naloxone (programmes) saved lives. UCB supported naloxone training programmes for families and carers run across England and initiated by local drug treatment services with the purpose of distributing and educating on the use of naloxone in an overdose emergency situation to save lives.

The service model developed by one of the local drug and alcohol teams cited in the poster and serviced by UCB, included supply of the product through a commercial pricing agreement.

The poster was presented as part of an internal UCB conference in the 'Power of Partnership' initiative, an internal award to recognise patient/NHS centred initiatives that showed collaboration across UCB, the NHS and patients with beneficial outcomes for all parties. Other posters were produced for the same award session by representatives operating in other therapeutic areas within UCB with the only purpose of sharing best practices that delivered patient benefit.

UCB sales and promotional activities

In 2012 take-home programmes were acknowledged in UK clinical practice and recommended as a measure to prevent opiate overdose-related deaths. UCB submitted that it supplied product in response to demand from this type of initiative.

UCB sales targets were based on the whole Minijet portfolio and there was no specific drive from the company to increase Naloxone Minijet use in the take-home setting. The incentive scheme at the time related to the full Minijet portfolio and not to naloxone particularly (UCB provided a copy of the incentive scheme document); this involved a national target with no specific sales targets at either key account manager or product level.

In the NHS, customer engagement was focussed on supply to meet demand with commercial pricing arrangements based on the full range of Minijet products. There was no interest in UCB product differentiation and UCB had not produced any material with this purpose. These products were clinically important generics, with a significant proportion of the engagement with customers in the procurement and purchasing pharmacy arenas, rather than clinical discussions.

In summary, UCB submitted that based on all the considerations above, there was no ground in the complainant's allegations for Clause 3 as naloxone Minijet had always been promoted within the terms of its licence. UCB therefore refuted a breach of Clause 9.1 as high standards had been maintained.

UCB submitted that the complainant had portrayed the use of the poster in a completely different way from both intention and actual use therefore UCB denied a breach of Clause 15.9.

Collectively in relation to all of the above, UCB submitted that it had never pursued a course of action that could bring discredit upon the pharmaceutical industry or harm patient safety and/or public health; therefore, it denied a breach of Clause 2.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure stated that anonymous complaints would be accepted, but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant could not be contacted for more information. The Panel noted the parties' interpretation of the licensed indication for naloxone Minijet differed.

The Panel noted that naloxone Minijet 400mcg/ml was indicated for the treatment of respiratory depression induced by natural or synthetic opioids. The medicine was presented as prefilled syringes of 1 or 2mls (400 or 800mcg). The usual initial adult dose was 400 - 2000mcg every 2 to 3 minutes if necessary. If no response was observed after the administration of 10mg then the depressive condition might be caused by a medicine or a disease process not responsive to naloxone. Treatment of overdose might thus require the use of a number of Minijet syringes. Use of naloxone Minijet in the non-medical setting was not referred to in the SPC and in that regard it did not appear that the product was specifically intended or packaged for such use and so non-medical responders might find it more difficult to use than other forms of naloxone, particularly Martindale's Prenoxad. Nonetheless, the Panel did not consider that take-home use of naloxone Minijet was off licence *per se* as alleged. No breach of Clause 3.2 was ruled.

The Panel disagreed with UCB's submission that the poster was not briefing material for the representatives; it had been presented at an internal UCB conference with the purpose of sharing best practice. The Panel assumed that as the poster had been developed by a representative, it mirrored what he/she considered was acceptable to claim about naloxone Minijet. The Panel noted that the poster did refer to training family friends, however it was extremely concerned that the title of the poster stated, without qualification, 'Minijet team Naloxone: How a Take Away Can Save Hundreds of Lives'. There was no reference cited in support of the statement and no indication as to the time period over which hundreds of lives would be saved by naloxone Minijet. Additional text stated that an overdose could now be referred to in the present tense: 'I have a friend who [overdosed] last week. Naloxone did that' which implied that naloxone saved the lives of everyone who overdosed. The poster also stated that naloxone Minijet provided the ideal offering, and in that regard the Panel noted its comments above about Prenoxad. The poster also stated that naloxone Minijet had the potential to dominate the market and that the dose of the competitor was too high. The Panel considered that the content of the poster was such that it advocated claims for take-home naloxone Minijet, or the competitor, which were likely to be in breach of the Code. A breach of Clause 15.9 was ruled. Overall the Panel considered that, given its content, the production of the poster showed poor judgement and in that regard it ruled a breach of Clause 9.1 as it considered that high standards had not been maintained.

The Panel noted its rulings and comments above and although it had some concerns, it did not consider that the circumstances were such as to rule a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

Complaint received **20 December 2017**

Case completed **27 March 2017**