CASE AUTH/3568/10/21

VOLUNTARY ADMISSION BY ROCHE

Typographical error regarding dosing within the Gazyvaro leavepiece

Roche made a voluntary admission in relation to a typographical dosing error in a Gazyvaro (obinutuzumab) leavepiece (ref M-GB-00000509) which the company submitted was for nurses.

Gazyvaro (obinutuzumab) was a Type II humanised anti-CD20 monoclonal antibody indicated for the treatment of certain patients with follicular lymphoma (FL) or chronic lymphocytic leukaemia (CLL). One vial of 40mL concentrate contained 1,000mg obinutuzumab, corresponding to a concentration before dilution of 25mg/mL.

Roche stated that the incorrect information about the Gazyvaro dose within the leavepiece at issue was in a chart on page 6 which set out the infusion rates for CLL patients. The chart gave information on the dose, Gazyvaro volume and final infusion volume for cycle 1, day 1, day 2, day 8 and day 15. It also had information for cycles 2-6. The front page of the leavepiece referred to the product by name, Gazyvaro, followed by 'checklist for the treatment of patients with follicular lymphoma (FL) & chronic lymphocytic leukaemia (CLL)'. The Gazyvaro dose for cycle 1 day 1 on page 6 was given as 1000mg instead of 100mg.

Roche stated that the error was identified by an employee on 1 September 2021. Roche submitted that all other values including the Gazyvaro volume, final infusion volume and the infusion rates were correct as were any other references to dosage contained within the leavepiece.

Roche stated that it was committed to the appropriate use of medicines, protecting the safety of patients and strove to maintain high standards in the ethical promotion of its medicines. As soon as this single typographical error was identified the leavepiece was immediately withdrawn from use and a full investigation initiated. Details were provided.

Roche submitted that Gazyvaro was launched onto the UK market in June 2015. The material in question was therefore not part of the launch materials which would have introduced the health professionals to the product, and *inter alia*, its dosing regimens. By 2019 the product could therefore be considered as more established on the UK market and its use and administration more familiar to UK hospital practices.

Roche stated that for a product such as Gazyvaro to be administered in hospital, well established and appropriate prescribing, procurement, preparation and administration procedures had to be in place. These procedures would be developed in line with the relevant data and safety information. Manufacturers' promotional items would have been most commonly utilised as an *aide memoire* for discussions with Roche representatives on infusion rates. It was therefore felt that the item in question would be sufficiently far

enough removed to have a direct impact on well-established practices and more importantly the administration of an incorrect dose. Were this item to be used to guide in procedural development, it would have been used in conjunction with other documentation such as the summary of product characteristics, hospital protocols, and relevant data sheets; the combination of which would have readily highlighted the typographical error.

Roche submitted that Gazyvaro was typically reconstituted and prepared by pharmacy or was outsourced to a compounding/aseptic unit. The primary audience for page 6 was a haematology nurse who would be involved in the administration of the product once reconstituted rather than the writing of a prescription or preparation of the product. As such the primary intent of page 6 was to detail the infusion rates that those administering the product would need to use to obtain the correct dose, rather than focus on the dose prescribed.

Roche stated that it had been considered that were a nurse to use this guide to draw up a dose, the volume of 4mL as per the volume stated in the column headed 'Gazyvaro volume (mL)' would result in the correct dose of 100mg rather than 1000mg given; Gazyvaro was a 25mg/mL solution. It was also noted that if this item were to be used to draw up a dose, the discrepancy between volume and dose would thus highlight the typographical error.

Upon review of the above and the wider investigation and following withdrawal and the permanent discontinuation of the material, it was deemed appropriate to notify the relevant health professionals who might have received the material containing the single typographical error and recommend its destruction. As such a communication in the form of a written letter identifying the material in question and outlining the single typographical error was sent to each unit in the UK with the potential to administer Gazyvaro.
In light of the above Roche considered this a breach of the Code on the basis that the information provided was inaccurate due to the single isolated typographical error.

Whilst it was identified that inadvertent human error had likely led to the single typographical error remaining present in the material at certification, Roche considered that the high standards expected of the company had not been maintained in breach of the Code.

Roche submitted that whilst it was regrettable to find a single isolated typographical error in a piece of material, it was confident following an exhaustive safety investigation that there was no direct impact to patient safety, and felt the immediate and robust actions taken through comprehensive investigation with corrective measures highlighted the high standards Roche constantly strove to maintain. As such Roche believed the high standards expected and confidence in the industry had been upheld.

The detailed response from Roche is given below.

The Panel noted that the leavepiece at issue was certified and approved for use on 22 July 2020. Roche submitted that the error was identified on 1 September 2021 as part of the printing of a new batch of leavepieces. Roche had instigated a withdrawal but as the existing stock had been distributed there was no stock returned by representatives.

Roche explained that health professionals were informed of the error on 6 October 2021 by a letter sent by post to haematology units in the UK which administered Gazyvaro. The units were selected by the account list covered by Roche representatives and those units purchasing the product.

The 14 page leavepiece first detailed dosing information for FL. Page 5 of the leavepiece set out the dosing and schedule for CLL patients. Page 5 was clear that for cycle 1 the first 1000mg was split over two infusion bags, with 100mg on day 1 followed by 900mg on day 1 if there were no infusion related symptoms. The 900mg dose would be given on day 2 if there were infusion related symptoms. Similar information was given about the rest of cycle 1 (with 1000mg on day 8 and day 15) and Day 1 of cycles 2-6. Page 5 gave no information about the Gazyvaro volume, the final infusion volume or infusion rates; it only referred to infusion bags.

The Panel noted the error on page 6 where the first dose of Gazyvaro was listed as 1000mg instead of 100mg. Roche submitted that it was an isolated error. The Panel noted Roche's submission regarding the accuracy of the other information on the page and the protocols and arrangements in hospitals regarding the preparation of Gazyvaro by the hospital pharmacist prior to its administration. It also noted Roche's submission that page 6 of the leavepiece was clear about the Gazyvaro volume for cycle 1, day 1; health professionals using the information about the Gazyvaro volume (4ml) would mean that the correct dose of 100mg would be used rather than 1000mg, given Gazyvaro was a 25mg/ml solution.

Pages 7 and 8 of the leavepiece were headed 'Preparing your FL and CLL Patient for their treatment' with page 8 including an additional section for CLL patients. This referred to the need to prepare CLL patients for the possibility of infusion related reactions (IRRs), particularly in advance of the first infusion on day 1 (and day 2 if infusion was split over 2 days) and the need to monitor the patient closely especially for the first 2 hours. The leavepiece also included information about premedication and managing IRRs.

The Panel was very concerned about the error on page 6 and considered that it could have led to patient safety issues, particularly as the error related to the first dose of the medicine. Page 6 was inaccurate and misleading. The Panel therefore ruled breaches of the Code including that high standards had not been maintained as acknowledged by Roche.

The Panel noted the actions taken by Roche once the error was discovered. These included withdrawing the leavepiece, informing health professionals of the error and checking the Roche safety database with regard to the impact of the error. Roche submitted that there was no evidence that the error in the leavepiece had resulted in an increase in reports of errors of administration in patients. The Panel noted that Clause 2 was reserved for use as a sign of particular censure and that the supplementary information to that clause listed prejudicing patient safety as an example of an activity likely to be in breach of Clause 2. The Panel noted that there was more than a year between certification of the material and identification of the error and that during that time more than five hundred hard copies of the leavepiece had been distributed to health professionals as well as electronic versions of the material downloaded from Roche's website. The Panel queried why it took Roche more than one month between identification of the error in the material and notification to health professionals of the

error. The Panel noted its comments and rulings above and considered that the dosing error in the material might have prejudiced patient safety and therefore a breach of Clause 2 was ruled.

Roche made a voluntary admission in relation to a typographical dosing error in a Gazyvaro (obinutuzumab) leavepiece (ref M-GB-00000509) which the company submitted was for nurses.

Gazyvaro (obinutuzumab) was a Type II humanised anti-CD20 monoclonal antibody indicated for the treatment of certain patients with follicular lymphoma (FL) or chronic lymphocytic leukaemia (CLL). One vial of 40mL concentrate contained 1,000mg obinutuzumab, corresponding to a concentration before dilution of 25mg/mL.

Roche stated that the incorrect information about the Gazyvaro dose within the leavepiece at issue was in a chart on page 6 which set out the infusion rates for CLL patients.

The chart gave information on the dose, Gazyvaro volume and final infusion volume for cycle 1, day 1, day 2, day 8 and day 15. It also had information for cycles 2-6. The front page of the leavepiece referred to the product by name, Gazyvaro, followed by 'checklist for the treatment of patients with follicular lymphoma (FL) & chronic lymphocytic leukaemia (CLL)'. The Gazyvaro dose for cycle 1 day 1 on page 6 was given as 1000mg instead of 100mg.

VOLUNTARY ADMISSION

Roche stated that on 1 September 2021 an employee identified an isolated singular typographical error in a promotional, certified, leavepiece (M-GB-00000509) intended for use by haematology specialist nurses. The item in question was a ring bound booklet of approximately A6 size.

Roche stated that there was a single isolated typographical error in the Gazyvaro dose column in the infusion rates chart for CLL on page 6 of the leavepiece where the Gazyvaro dose should state 100mg for cycle 1, day 1 rather than 1000mg. Roche submitted that all other values including the Gazyvaro volume, final infusion volume and the infusion rates were correct as were any other references to dosage contained within the leavepiece.

Roche stated that it was committed to the appropriate use of medicines, protecting the safety of patients and strove to maintain high standards in the ethical promotion of its medicines. As soon as this single typographical error was identified the leavepiece was immediately withdrawn from use and a full investigation initiated.

An immediate notification to Roche representatives was issued to implement immediate cessation of use. This was then followed up with a formal withdrawal of the material in question as per Roche standard operating procedures for the withdrawal of promotional items. A communication to all those trained in the use of the material was provided along with a detailed briefing document (M-GB-00004988, copy provided). Roche submitted that it conducted a review of all remaining Gazyvaro material which highlighted that this was an isolated finding across all Gazyvaro materials.

The UK Qualified Person for Pharmacovigilance was informed and a full and comprehensive investigation involving both UK and Global safety teams was initiated to assess any impact on patient safety.

Upon interrogation of the Global Roche safety database, the safety teams concluded from the reports of medication in association with obinutuzumab received into the Roche safety database since 1 May 2019 that, there was no evidence that the typographical error in the nurses' leavepiece had resulted in an increase of errors of administration in patients.

Roche submitted that Gazyvaro was launched onto the UK market following reimbursement by NICE in June 2015. The material in question was therefore not part of the launch materials which would have introduced the health professionals to the product, and *inter alia*, its dosing regimens. By 2019 the product could therefore be considered as more established on the UK market and its use and administration more familiar to UK hospital practices.

Roche stated that for a product such as Gazyvaro to be administered in hospital, well established and appropriate prescribing, procurement, preparation and administration procedures had to be in place. These procedures would be developed in line with the relevant data and safety information. Manufacturers' promotional items would have been most commonly utilised as an *aide memoire* for discussions with Roche representatives on infusion rates. It was therefore felt that the item in question would be sufficiently far enough removed to have a direct impact on well-established practices and more importantly the administration of an incorrect dose. Were this item to be used to guide in procedural development, it would have been used in conjunction with other documentation such as the summary of product characteristics, hospital protocols, and relevant data sheets; the combination of which would have readily highlighted the typographical error.

Roche submitted that Gazyvaro was typically reconstituted and prepared by pharmacy or was outsourced to a compounding/aseptic unit. The primary audience for page 6 was a haematology nurse who would be involved in the administration of the product once reconstituted rather than the writing of a prescription or preparation of the product. As such the primary intent of page 6 was to detail the infusion rates that those administering the product would need to use to obtain the correct dose, rather than focus on the dose prescribed.

Roche stated that it had been considered that were a nurse to use this guide to draw up a dose, the volume of 4mL as per the volume stated in the column headed 'Gazyvaro volume (mL)' would result in the correct dose of 100mg rather than 1000mg given Gazyvaro was a 25mg/mL solution. It was also noted that if this item were to be used to draw up a dose, the discrepancy between volume and dose would thus highlight the typographical error.

Upon review of the above and the wider investigation and following withdrawal and the permanent discontinuation of the material, it was deemed appropriate to notify the relevant health professionals who might have received the material containing the single typographical error and recommend its destruction. As such a communication in the form of a written letter identifying the material in question and outlining the single typographical error was sent to each unit in the UK with the potential to administer Gazyvaro (M-GB-00005036, copy provided).

Roche submitted that it strove to uphold the highest of standards and believed learning from such situations was paramount to prevent any recurrence. Whilst the individuals responsible for certifying the material in question were no longer in the company, the importance of attention to detail when certifying material was being flagged and shared learnings were being rolled out across the business.

In light of the above Roche considered this a breach of Clause 6.1 on the basis that the information provided was inaccurate due to the single isolated typographical error.

Whilst it was identified that inadvertent human error had likely led to the single typographical error remaining present in the material at certification, Roche considered that the high standards expected of the company had not been maintained in breach of Clause 5.1.

Roche submitted that whilst it was regrettable to find a single isolated typographical error in a piece of material, it was confident following an exhaustive safety investigation that there was no direct impact to patient safety and felt the immediate and robust actions taken through comprehensive investigation with corrective measures highlighted the high standards Roche constantly strove to maintain. As such Roche believed the high standards expected and confidence in the industry had been upheld.

When writing to Roche, the Authority asked it to consider the requirements of Clauses 2,5.1 and 6.1 of the 2021 Code.

RESPONSE

Roche explained that there were 550 leave pieces distributed by company representatives. In September 2021 there was a request for a print run as all available stock had been issued to health professionals. A new batch of 50 were sent to print, however the typographical error was identified before these were issued to representatives. As the existing stock had been distributed there was no stock returned back to Roche's distribution warehouse.

In addition to those distributed by company staff a further 16 were downloaded directly from Roche's health professional resource website.

Roche provided a copy of the certificate for the leavepiece as well as a copy of the Gazyvaro SPC. The qualifications of the final signatories were also provided.

The follow up letter advising health professionals of the error was sent by post on 6 October 2021 to 234 haematology units in the UK with the potential to administer Gazyvaro. These units were selected based on the account list covered by Roche field representatives and units that were purchasing Gazyvaro. Since then Roche had not received any requests for additional information either via its medical information team or Roche representatives.

In addition to Roche's consideration of the requirements of Clauses 5.1 and 6.1 in its original correspondence, those relating to Clause 2 were outlined below.

Roche submitted that it recognised the special nature of the medicine and the professional standing of the audience.

On identification of this issue the intended audience were contacted via a targeted communication, configured and appropriately tailored to said audience to notify them of the error without delay, with every subsequent effort being made to remove and destroy the material in question and reinforce the correct information and reference material.

The matter was managed with a sense of urgency and priority to reflect the special nature of the medicine and the therapeutic area in which it was used, as reflected by the timelines of the Roche internal review and external actions.

A root cause analysis was underway to identify and correct the root cause of the typographical error to ensure that this inadvertent error was not replicated in the future.

Roche submitted that it conducted a thorough investigation to quantify any risk to patient safety as a result of the one-off, single instance typographical error in an isolated promotional piece.

A thorough local and global clinical safety review was undertaken to quantify the degree of risk to patient safety and was documented accordingly.

Roche stated that this review was complemented by a detailed query of the Roche safety database to quantify any dosing errors that might have occurred as a result of the single one-off typographical error in the isolated promotional piece and was documented accordingly.

The net outcome of the review reassuringly characterised an extremely low risk to patient safety, complemented by the observation that the distribution and use of the promotional piece in question was far removed from the medicine reconstitution mechanisms that routinely operated in the hospital pharmacies.

Roche stated that it was committed to maintaining high standards and learning from instances of inadvertent human error.

This singular occurrence of an isolated typographical error in an isolated promotional piece was the result of inadvertent and unintentional human error, which upon identification was characterised, investigated and corrected with a sense of urgency and priority.

A thorough internal root-cause analysis and review was underway to ensure that the risk of replicating this unintentional error in the future was minimised to the greatest extent possible.

This remained an isolated typographical error in a singular promotional piece and not a series of cumulative breaches of a similar and serious nature in the same therapeutic area within a short space of time.

In summary and in good faith, Roche was of the view that this specific error did not meet the established criteria for a Clause 2 breach as defined in the Code and further clarified in published cases of historic Clause 2 breaches.

PANEL RULING

The Panel noted that the leavepiece at issue was certified and approved for use on 22 July 2020. Roche submitted that the error was identified on 1 September 2021 as part of the printing of a new batch of leavepieces. Roche had instigated a withdrawal but as the existing stock had been distributed there was no stock returned by representatives. Roche explained that health professionals were informed of the error on 6 October 2021 by a letter sent by post to haematology units in the UK which administered Gazyvaro. The units were selected by the account list covered by Roche representatives and those units purchasing the product.

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The Panel was very concerned about the error on page 6 and considered that it could have led to patient safety issues, particularly as the error related to the first dose of the medicine. Page 6 was inaccurate and misleading. The Panel therefore ruled a breach of Clause 6.1 of the 2021 Code as acknowledged by Roche. The Panel also considered that high standards had not been maintained and a breach of Clause 5.1 of the 2021 Code was ruled as acknowledged by Roche.

The Panel noted the actions taken by Roche once the error was discovered. These included withdrawing the leavepiece, informing health professionals of the error and checking the Roche safety database with regard to the impact of the error. Roche submitted that there was no evidence that the error in the leavepiece had resulted in an increase in reports of errors of administration in patients. The Panel noted that Clause 2 was reserved for use as a sign of particular censure and that the supplementary information to that clause listed prejudicing patient safety as an example of an activity likely to be in breach of Clause 2. The Panel noted that there was more than a year between certification of the material and identification of the error and that during that time more than five hundred hard copies of the leavepiece had been distributed to health professionals as well as electronic versions of the material downloaded from Roche's website. The Panel queried why it took Roche more than one month between identification of the error in the material and notification to health professionals of the error. The Panel noted its comments and rulings above and considered that the dosing error in the material might have prejudiced patient safety and therefore a breach of Clause 2 was ruled.

Complaint received **6 October 2021**

Case completed **7 December 2021**