CASE AUTH/3340/4/20

COMPLAINANT v VIIV HEALTHCARE

Out of date prescribing information

A complainant who described him/herself as a concerned UK health professional, complained that a document downloaded from a promotional ViiV website contained out-of-date prescribing information for Dovato (dolutegravir and lamivudine), Juluca (dolutegravir and rilpivirine), Triumeq (dolutegravir, abacavir and lamivudine) and Tivicay (dolutegravir) in that a contraindication for dolutegravir recently added to the summary of product characteristics (SPC) was missing. The complainant stated that this was clearly a patient safety issue.

Dovato, Juluca, Triumeq and Tivicay were all variously indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in certain adults, adolescents and children.

The detailed response from ViiV is given below.

The Panel noted ViiV's submission that the variation for the update to include the new contraindication for dolutegravir was submitted to the European Medicines Agency (EMA) as part of a procedure whereby non-complex variations that affected a number of marketing authorizations could be submitted together to reduce the administrative burden; dolutegravir was included in four of ViiV's medicines. The SPCs for the four medicines (Tivicay, Dovato, Juluca and Triumeq) detailed ViiV Healthcare BV, Netherlands as the marketing authorization holder.

The Panel noted ViiV's submission that the EMA formally notified the marketing authorization holder of the approval of the variation on 14 April 2020 which was when the company could consider the variations ready for implementation. However, the Panel noted ViiV's submission that it was GlaxoSmithKline's (ViiV's parent company) policy to ensure that the updated SPCs and European Commission approval documents were published in all EU languages on the European Commission website, managed by the European Commission and therefore out of ViiV's control, before the local operating companies were notified to implement product changes. The Tivicay, Dovato and Juluca documents were published on the European Commission website on 15 April and the changes were enacted by ViiV UK on 24 April (within 7 working days). However, ViiV UK did not update the document in question, which referred to Tivicay, Dovato, Juluca and Triumeq, until 1 May as publication of the details for Triumeq on the European Commission website was delayed until 27 April.

The Panel noted that whilst the company could consider the variations approved and ready for implementation on 14 April, the document at issue was not updated until 1 May. The Panel noted, therefore, that on the date that the complaint was submitted (29 April), the document on the ViiV exchange website contained out-of-date prescribing information for Dovato, Juluca, Triumeq and Tivicay in that it omitted a recently added

contraindication. Therefore, as acknowledged by ViiV, the prescribing information was inconsistent with the SPC current at that time and a breach of the Code was ruled. High standards had not been maintained and a further breach of the Code was ruled.

The Panel noted that whilst the variations were approved and ready for implementation on 14 April, GlaxoSmithKline's policy was to wait for relevant documents to be published in all EU languages on the European Commission website before it notified the local operating companies to implement product changes. While no details were provided with regards to the reason for this approach, the Panel noted that the publication of the Tivicay, Dovato and Juluca documents had occurred only one day after the marketing authorization holder was formally notified of the approval of the variation and therefore this step did not appear to have a significant delaying effect on the timelines in normal circumstances. The Panel noted, however, that this step was outside of ViiV's control and there was a delay in the publication of the Triumeq documents which led to a delay in the updating of the document at issue which contained the prescribing information for all four products.

The Panel noted ViiV's submission that it was already in the process of updating the prescribing information for all of its dolutegravir products on the website and the prescribing information displayed for the individual products, Dovato, Juluca and Tivicay were up-to-date by 29 April 2020 and reflected the new contraindication. According to ViiV, there were no other promotional items related to Triumeq live at the time.

The Panel noted that ViiV had processes in place to ensure prescribing information was up-to-date and once notified, following publication of the Triumeq documents on the European Commission website, ViiV UK updated the document at issue within four working days which was within thirteen working days from the formal notification by the EMA. The Panel considered that the particular circumstances of this case did not warrant a ruling of a breach of Clause 2 and no breach was ruled.

A complainant who described him/herself as a concerned UK health professional, complained that a document downloaded from the ViiV exchange website contained out-of-date prescribing information for Dovato (dolutegravir and lamivudine), Juluca (dolutegravir and rilpivirine), Triumeq (dolutegravir, abacavir and lamivudine) and Tivicay (dolutegravir). ViiV exchange was a promotional website for health professionals hosted by ViiV Healthcare UK Limited. Dovato, Juluca, Triumeq and Tivicay were all variously indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in certain adults, adolescents and children.

COMPLAINT

The complainant noted that the prescribing information for dolutegravir on the ViiV Exchange website was updated in April 2019; the latest summary of product characteristics (SPC) on the electronic Medicines Compendium (eMC) website, however, was dated April 2020. In that regard, the complainant noted an addition to Section 4.3, Contraindications, in relation to co-administration with medicines with narrow therapeutic windows, that were substrates of organic cation transporter (OCT) 2, including fampridine.

The complainant stated that as patients who were HIV positive often had considerable polypharmacy, this was clearly a patient safety issue.

The complainant noted that dolutegravir was present in many of ViiV's products and thus alleged that all of the prescribing information for products which contained that medicine were out-of-date. This was, therefore, no small matter and it was very worrying that such a key change could take place without the company ensuring that all materials were updated.

The complainant stated that he/she had neither the time nor the inclination to trawl the entire web to cross-check every single prescribing information, but if the main prescribing information on the main website was wrong, he/she doubted that others had been updated. The complainant accepted that he/she had no evidence to raise a complaint in that regard *per se*, but asked that the company check everything else since this was quite a significant patient safety issue and if the company was giving out materials to individuals with the wrong safety data, it was quite serious.

When writing to ViiV, the Authority asked it to consider the requirements of Clauses 4.1, 9.1 and 2 of the Code.

RESPONSE

As background, ViiV submitted that the described pdf document contained prescribing information for four different ViiV products, with each product having dolutegravir (DTG) as its core medicine. These products were Dovato (DTG and lamivudine), Juluca (DTG and rilpivirine), Triumeq (DTG, abacavir and lamivudine) and Tivicay (DTG on its own).

ViiV stated that it took patient safety extremely seriously and had clear processes in place to ensure prescribing information was up-to-date for its products. Nevertheless, ViiV did not dispute the complainant's central observation that the document, which contained the prescribing information for four of its medicines and accessed via the ViiV exchange website on what the company assumed was 29 April (the date the complainant was submitted), did not include the information about a new contraindication for DTG, ie that it must not be administered concurrently with medicines which had narrow therapeutic windows that were substrates of OCT 2, including, but not limited to, fampridine. ViiV stated that it sincerely regretted what had happened and had investigated why this specific incident occurred; it had examined both external and internal factors that might have contributed to it and had taken steps to address any issues urgently as detailed below.

ViiV noted that it was already in the process of updating the prescribing information for all of its DTG products on the website and the prescribing information displayed for the individual products, Dovato, Juluca and Tivicay, which the complainant acknowledged he/she did not check, were in fact already up-to-date by 29 April 2020.

ViiV stated that the variation for the update to prescribing information was submitted to the European Medicines Authority (EMA) as part of the EMA work sharing procedure whereby non-complex variations that affected a number of marketing authorizations (MAs) could be submitted together to reduce the administrative burden on both sides. ViiV undertook a work sharing procedure given DTG was present in all four medicines.

In a workshare process, notification that the variation was approved was queued until all products within the work sharing arrangement had been processed. In this case, although Dovato, Triumeq and Juluca gained Commission Decision on 1 April, Tivicay did not receive it until 8 April. These were the dates that appeared on the SPCs. However, the formal

notification of the approval of the variation itself to the market authorization holder by the EMA occurred on 14 April. It was at that point the company could consider the variations approved and ready for implementation. ViiV submitted that its investigation showed that it was the policy of GlaxoSmithKline (ViiV's parent company) to ensure that the updated SPCs and European Commission approval documents were published in all EU languages in the Union Register on the European Commission website before the local operating companies were notified to implement product changes. Publication of these documents on the website was managed by the European Commission and was outside of ViiV's control. In this case, publication occurred on 15 April for Tivicay, Dovato and Juluca but not until 27 April for Triumeq due to an error in the wording in Section 4.4 (Special warnings and precautions for use) of the SPC. This error needed to be corrected before publication (and the EMA was less responsive during this time due to its active involvement in the COVID-19 situation) resulting in the delay to 27 April.

The ViiV/GlaxoSmithKline standard operating procedure (SOP) for prescribing information updates required local operating companies to make changes within 10 working days of notification by the internal regulatory team for a target safety category 2 (TSC 2) change, described internally as 'A change to the SPC resulting in current materials becoming inconsistent with the particulars listed in the SPC'. A TSC 2 was not as urgent as a TSC 1 ('An urgent /serious safety related change and/or product recall requiring immediate action by local operating companies'), which required changes within 24 hours. Following notification on 15 April, these changes were duly enacted by ViiV UK for Tivicay, Dovato and Juluca on 24 April, and therefore in 7 working days. Nevertheless, as the item in question contained four sets of prescribing information, each relating to a different ViiV product, including Triumeq, the item was not immediately updated but queued until the final Triumeq publication occurred. This occurred on 27 April and ViiV UK updated the item on 1 May, ie in 4 working days.

As a result, and when viewed on 29 April 2020, the combined prescribing information for the item at issue did not reflect the update and showed April 2019 at the end of the document, the last previous update of the Tivicay prescribing information. ViiV submitted that all of the other prescribing information on the website had already been updated by that time and reflected the new contraindication. There were no other promotional items related to Triumeq live at the time. ViiV provided a summary of the regulatory timelines.

ViiV stated that it was committed to patient safety and understood the importance of maintaining up-to-date prescribing information. In its view, some external factors played a role on this occasion such that the dates on the SPCs did not actually reflect the dates on which GlaxoSmithKline was notified of the decisions and could act upon them. The company requested that the Panel consider these factors when reaching a conclusion on the time taken to update the prescribing information.

ViiV stated that it was also clear that the internal GlaxoSmithKline process of waiting for final publication on the European Commission website added to the delay for Triumeq and subsequently the item at issue. ViiV submitted that whilst it had acted within its internal obligations, the broader internal process led to a delay in the prescribing information. This issue had already, and urgently, been escalated internally with a view to amending the process such that ViiV was informed immediately and did not need to wait for the publication of the translated documents by the European Commission on its website before updating the prescribing information.

PANEL RULING

The Panel noted ViiV's submission that the variation for the update to include the new contraindication for DTG was submitted to the EMA as part of a work sharing procedure, whereby non-complex variations that affected a number of marketing authorizations could be submitted together to reduce the administrative burden on both sides; DTG was included in four of ViiV's medicines. The SPCs for the four medicines (Tivicay, Dovato, Juluca and Triumeq) detailed ViiV Healthcare BV, Netherlands as the marketing authorization holder.

The Panel noted ViiV's submission that the EMA formally notified the marketing authorization holder of the approval of the variation on 14 April 2020 which was when the company could consider the variations ready for implementation. However, the Panel noted ViiV's submission that it was GlaxoSmithKline's (ViiV's parent company) policy to ensure that the updated SPCs and European Commission approval documents were published in all EU languages on the European Commission website, managed by the European Commission and therefore out of ViiV's control, before the local operating companies were notified to implement product changes. The Tivicay, Dovato and Juluca documents were published on the European Commission website on 15 April and following notification on the same day, the changes were enacted by ViiV UK on 24 April (within 7 working days). However, ViiV UK did not update the document in question, which referred to Tivicay, Dovato, Juluca and Triumeq, until 1 May as publication of the details for Triumeq on the European Commission website was delayed until 27 April due to an error in Section 4.4 Special warnings and precautions for use of the SPC which was thus unrelated to the contraindication at issue which was detailed in Section 4.3.

The Panel noted that prescribing information (defined by Clause 4.2) must be up-to-date and comply with Clauses 4.1 and 4.2 of the Code which included providing a succinct statement of, among other things, contraindications giving in an abbreviated form the relevant information in the SPC. The prescribing information must be consistent with the SPC for the medicine.

The Panel noted that whilst the company could consider the variations approved and ready for implementation on 14 April, the document at issue was not updated until 1 May. The Panel noted, therefore, that on the date that the complaint was submitted (29 April), the document on the ViiV exchange website contained out-of-date prescribing information for Dovato, Juluca, Triumeq and Tivicay in that it omitted the contraindication that DTG must not be administered concurrently with medicines which had narrow therapeutic windows that were substrates of OCT 2, including, but not limited to, fampridine. Therefore, as acknowledged by ViiV, the prescribing information was inconsistent with the SPC current at that time and a breach of Clause 4.1 was ruled.

The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that whilst the variations were approved and ready for implementation on 14 April, GlaxoSmithKline's policy was to wait for the updated SPCs and European Commission approval documents to be published in all EU languages on the European Commission website before it notified the local operating companies to implement product changes. While no details were provided with regards to the reason for this approach, the Panel noted that the publication of the Tivicay, Dovato and Juluca documents had occurred only one day after the marketing authorization holder was formally notified of the approval of the variation and therefore this step did not appear to have a significant delaying effect on the timelines in normal circumstances. The Panel noted, however, that this step was outside of ViiV's control and there was a delay in

the publication of the Triumeq documents which led to a delay in the updating of the document at issue which contained the prescribing information for all four products.

The Panel noted ViiV's submission that it was already in the process of updating the prescribing information for all of its DTG products on the website and the prescribing information displayed for the individual products, Dovato, Juluca and Tivicay were up-to-date by 29 April 2020 and reflected the new contraindication. According to ViiV, there were no other promotional items related to Triumeq live at the time.

The Panel noted that ViiV had processes in place to ensure prescribing information was up-to-date and once notified, following publication of the Triumeq documents on the European Commission website, ViiV UK updated the document at issue within four working days which was within thirteen working days from the formal notification by the EMA. The Panel considered that the particular circumstances of this case did not warrant a ruling of a breach of Clause 2 and no breach was ruled.

Complaint received **30 April 2020**

Case completed **10 July 2020**