GILEAD SCIENCES v VIIV HEALTHCARE

Promotion of Tivicay and Juluca

Gilead Sciences Europe complained about materials being used by ViiV Healthcare to promote Tivicay (dolutegravir) and Juluca (dolutegravir/rilpivirine).

The detailed response from ViiV is given below.

1 Alleged off-label promotion of Tivicay

Gilead stated that during the HIV Drug Therapy conference held in Glasgow, 28-31 October 2018, ViiV promoted results from the GEMINI-1 and GEMINI-2 studies which investigated the efficacy and safety of dolutegravir (DTG) in combination with one other antiretroviral (ARV) agent, lamivudine (3TC), for the treatment of HIV in treatment naïve patients and alleged that this was not in accordance with the marketing authorization and was inconsistent with the SPC for Tivicay at that time.

Gilead did not refer to specific materials but provided photographs of exhibition panels which it sated were 'some examples'. The Panel therefore considered the allegation in general and not in the context of any specific materials.

The Panel noted that the indication in Section 4.1 of the Tivicay SPC stated:

> **'Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children above 6 years of age'.**

The Panel noted that the indication in Section 4.1 did not specify a minimum or a maximum number of ARV medicines that Tivicay should be combined with. Section 4.2 (posology and method of administration) stated that Tivicay should be prescribed by physicians experienced in the management of HIV infection. Section 5.1 (pharmacodynamic properties) referred to various combinations of DTG with other ARV medicines including 3TC.

The Panel noted Gilead's assertation that at the time Tivicay was granted a marketing authorization for the above indication, no data existed on the use of DTG in combination with one other ARV agent in HIV treatment naïve patients.

The Panel noted that at the time of the conference, the Tivicay SPC did not refer to the GEMINI studies. According to ViiV, following the conference, in November 2018, the SPC was updated to include, *inter alia*, GEMINI-1 and GEMINI-2 study results in Section 5.1 and information based on these studies was included in Section 4.4 (special warnings and precautions for use) which stated:

> **'Lamivudine and dolutegravir**
> **The two-drug regimen of dolutegravir 50 mg once daily and lamivudine 300 mg once daily was explored in two large randomized and blinded studies, GEMINI 1 and GEMINI 2 (see section 5.1). This regimen is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine'.**

In the Panel's view it was not necessarily unacceptable to promote a medicine using studies that were not listed in its SPC as long as such data was not inconsistent with the particulars listed in the SPC. In the Panel's view, using Tivicay in combination with one other ARV medicine in HIV was not in itself inconsistent with the indication for Tivicay to be used in combination. Physicians might decide not to use a two drug-regimen prior to the availability of data.

The Panel noted its comments above and considered that Gilead had not proved, on the balance of probabilities, that ViiV's promotion of Tivicay in combination with lamivudine at the October 2018 conference in general, constituted promotion of Tivicay outside the terms of its marketing authorization or in a manner that was inconsistent with its SPC. No breach of the Code was ruled. The Panel did not consider that ViiV had failed to maintain high standards and ruled no breach of the Code.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted its rulings of no breach above and consequently ruled no breach of Clause 2.

2 Alleged use of Tivicay data in combination with two antiretroviral agents to support promotion of Tivicay with one antiretroviral agent

Gilead alleged that the claim 'Only dolutegravir has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens', available on the UK ViiV Exchange website, when used in the context of the promotion of two drug regimens, was misleading and incapable of substantiation.

Gilead also alleged that the claim 'Unbeaten in head to head clinical trials', made at the ViiV stand during the Glasgow HIV conference, was ambiguous, misleading, gave the impression that the attributes of DTG seen in triple therapy studies were also delivered when DTG was used as part of a two-drug regimen, and did not compare medicines for the same needs or intended for the same purpose.

The Panel noted that item VIIV/DTGRPV/0033/18(3) was a webpage on the ViiV exchange website with a focus on 2-drug regimens. The webpage included the subheading 'What makes DTG an ideal core agent to power a 2DR [2-drug regimen]?'. Below this, in smaller font, it stated 'Only dolutegravir…' followed by a number of claims including: 'Has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens'; and 'Is PROVEN EFFECTIVE in 2-drug regimens with lamivudine in treatment-naïve adult patients at 48 weeks and rilpivirine in virologically suppressed patients at 100 weeks'. 'SUPERIOR EFFICACY' and 'PROVEN EFFECTIVE' in the above two claims were in a different coloured font to the surrounding text.

The Panel noted that below this section of the webpage was a 'learn more' section which stated 'Explore dolutegravir-based, 2-drug regimens for your diverse patient needs' followed by the logos for Tivicay + lamivudine and Juluca.

The Panel noted that both the Tivicay and the Juluca SPCs stated that these medicines should be prescribed by physicians experienced in the management of HIV infection. The Panel considered the immediate and overall impression to an HIV physician. In the Panel's view, although the claim in question featured on a webpage promoting DTG-based 2-drug regimens, it appeared beneath the question of what made DTG an ideal core agent to power a 2-drug regimen. In the Panel's view it was clear that 'SUPERIOR EFFICACY' in the claim 'Only dolutegravir…Has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens' was in relation to DTG as a core agent in a 3-drug regimen and not in relation to a 2-drug regimen as alleged. An associated claim stated that DTG was '…PROVEN EFFECTIVE…' in two specific 2-drug regimens in certain patients. In this regard, the Panel considered that the intended audience would not be misled as alleged. Gilead had not shown, on the balance of probabilities, that the claim 'Only dolutegravir…Has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens' was misleading or incapable of substantiation as alleged and the Panel therefore ruled no breach of the Code.

The Panel did not consider that ViiV had failed to maintain high standards in this regard and ruled no breach of the Code.

The Panel noted that the claim 'Unbeaten in head to head clinical trials' appeared on an interactive ViiV stand panel at the HIV Drug Therapy 2018 conference, and directly below the claim, in smaller font, it stated 'Tap to explore the dolutegravir (DTG) data'. To the left of the heading was a circle that stated 'Powered by DTG at the core'. Below this were three large circles which were labelled: GEMINI-1 and GEMINI-2 data, SWORD-1 and SWORD-2 data, and depth and breadth of DTG clinical trials. When the circles were accessed, further information about the studies was provided, including that the GEMINI and SWORD studies were non-inferiority studies and evaluated DTG as part of a 2-drug regimen and that 10 studies, including superiority and non-inferiority studies, evaluated DTG as part of a 3-drug regimen.

That Panel considered that the first screen of the interactive stand panel needed to stand alone as not all individuals would stop to click through the screens and read the supporting information.

The Panel noted ViiV's submission that in every phase 3, head to head study that DTG had been included in, the results had either shown DTG based regimens to be superior or non-inferior in comparison with regimens based on other ARVs and that no combination of ARVs had shown superiority over a DTG-based regimen in any head-to-head clinical trial in any patient population.

In the Panel view, the word 'unbeaten' would imply to the audience that DTG was unsurpassed in any head-to head clinical trials and not necessarily that it had superior efficacy or had surpassed its comparators.

The Panel noted that the interactive screens on the stand panel predominantly referred to DTG-based 2-drug regimens which were evaluated in non-inferiority studies (SWORD-1, SWORD-2, GEMINI-1 and GEMINI-2). In the Panel's view, non-inferiority studies evaluated whether one treatment was non-inferior to another treatment by a pre-specified margin. In this regard, the Panel queried the use of 'unbeaten' in the claim given that the material predominantly referred to DTG-based 2-drug regimens which were only supported by non-inferiority studies. This was reinforced by the layout and reading left to right would mean viewing the non-inferiority data first. Context was important. The Panel considered that the claim on the stand panel in question which was immediately followed by 'Tap to explore the dolutegravir (DTG) data' encompassed all DTG clinical trials, including DTG-based 3-drug regimens which had been evaluated in both superiority and non-inferiority studies. The Panel therefore considered the body of evidence for the claim ie both 2-drug and 3-drug DTG based regimens noting that there were a number of studies.

The Panel noted that Gilead had provided no evidence to suggest that there were ARV combinations that had surpassed either a 2-drug or a 3-drug DTG-based regimen in any head-to-head clinical trial.

The Panel noted that the screen in question contained no details of the patient populations in the studies and a user would have to click on the screen to access such information. In the Panel's view, this was not necessarily unacceptable provided that the information on the screen in question was not misleading. The Panel noted that both the Tivicay and the Juluca SPCs stated that these medicines should be prescribed by physicians experienced in the management of HIV infection.

The Panel noted its comments above and considered that although the claim 'Unbeaten in head to head

clinical trials' was a strong, broad claim, there appeared to be data to support it and the audience would not be misled. Gilead had not shown, on the balance of probabilities, that the claim on the stand panel in question was ambiguous, misleading or incapable of substantiation as alleged and the Panel therefore ruled no breach of the Code. The Panel did not consider that ViiV had failed to maintain high standards in this regard and ruled no breach of the Code.

Gilead Sciences Europe Ltd complained about materials being used by ViiV Healthcare UK Ltd to promote Tivicay (dolutegravir) and Juluca (dolutegravir/rilpivirine). Tivicay was used in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV). Juluca was used in the treatment of HIV-1 infection in certain adults who were virologically-suppressed on a stable antiretroviral regimen for at least six months.

1 Alleged off-label promotion of Tivicay

COMPLAINT

Gilead stated that during the HIV Drug Therapy conference held in Glasgow, 28-31 October 2018, in the context of Tivicay promotion, ViiV promoted results from the GEMINI-1 and GEMINI-2 studies which investigated the efficacy and safety of dolutegravir (DTG) in combination with one other antiretroviral (ARV) agent, lamivudine (3TC), for the treatment of HIV in treatment naïve patients. Various claims accompanied the promotion of this combination (photographs of various exhibition panels were provided which included references to a two-drug regimen).

At the time of that promotion, Section 5.1 of the Tivicay summary of product characteristics (SPC) made reference to the following clinical studies, none of which investigated the use of DTG in combination with 3TC or any other combination of DTG with only one other ARV ('DTG based 2 drug regimens' or 'DTG based dual therapy') in treatment naïve patients:

- SINGLE (Walmsley et al (2013)) and SPRING-2 (Raffi et al (2013)) – studies of Tivicay once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), abacavir (ABC) and 3TC in HIV treatment naïve patients (ie 'DTG-based 3 drug regimens', alternatively named 'DTG-based triple therapy')
- FLAMINGO (Clotet et al (2014)) – study of Tivicay once daily in combination with two NRTIs (either ABC/3TC or emtricitabine/tenofovir disoproxil fumarate [FTC/TDF]) in HIV treatment naïve patients (ie a DTG-based 3 drug regimen, alternatively named DTG-based triple therapy)
- SAILING (Cahn et al (2013)– study of Tivicay once daily in combination with investigator selected background regimen consisting of up to 2 agents (including at least one fully active agent) in patients with prior treatment failure, but not exposed to the integrase class. The majority of patients were also taking a protease inhibitor [PI] in combination with Tivicay in this study.
- VIKING-3 (Castagna et al (2014)) – study of Tivicay 50mg twice daily in HIV-1 infected, ART-experienced adults with virological failure and current or historical evidence of raltegravir and/ or elvitegravir resistance (each being members of the integrase inhibitor class of ARVs). Patients received Tivicay 50 mg twice daily with the current failing background regimen for 7 days followed by optimised background ART from Day 8.

Gilead stated that on the first day of the conference (28 October), it contacted ViiV and asserted that the use of DTG in combination with only 3TC in the treatment of HIV was clearly off label, not in accordance with the terms of the Tivicay marketing authorization, and therefore in breach of Clause 3.2 of the Code. Gilead requested that any relevant material be removed immediately. ViiV's defence on site was that Tivicay could be promoted in combination with 3TC due to the so called 'broad' indication for Tivicay, namely 'Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children above 6 years of age'. As a result, ViiV did not agree to remove reference to any claims pertaining to the combination of Tivicay with 3TC, and so these were consequently available for the duration of the conference. Gilead further alleged a breach of Clauses 2 and 9.1 of the Code.

Gilead stated that ViiV's major defence was centered on Tivicay having a so called 'broad' indication, asserting that dolutegravir could be used under any circumstances, as long as with at least one other antiretroviral agent. This position was clearly not supportable for the following reasons:

(i) The SPC contained essential information for the use of a medicine, agreed after a process of evaluation and based on the clinical trials presented as part of the marketing authorization application.

The structure and content of the SPC were harmonised in the European Union and the basic principles for the presentation of the information in the SPC were set out in the 'Guideline on Summary of Product Characteristics' of the European Commission.

For the therapeutic indication (Section 4.1), the European regulators had resolved that the indication should be stated clearly and concisely and should define the target disease or condition, the age group, distinguishing between treatment (curative/ symptomatic), prevention and diagnostic indication. In order to maintain the indications as concise as possible, it was resolved at the regulatory level in Europe that the data of the studies, must be included in Section 5.1, not in Section 4.1, of the SPC.

In this manner, the relevant clinical information supporting the authorised indication, in particular, the results of the clinical trials assessed by the regulatory bodies which support the authorised

indication(s), should be concisely presented in Section 5.1 of the SPC. The aim of Section 5.1 was to present information that was relevant to prescribers and healthcare professionals about the authorised indication to ensure that the medicine was used in an efficient and safe manner in clinical practice.

The interpretation of the conditions of authorised use should, therefore, not be based on the information contained in a single section of the SPC in isolation, but require the review of the SPC as a whole, as the relevant scientific information was found in different sections.

(ii) At the time Tivicay was granted a marketing authorization by the European Medicines Agency (EMA) with the aforementioned indication, no data existed on the use of dolutegravir in combination with one other antiretroviral agent in HIV treatment naïve patients. In fact, at that time, there were no antiretroviral regimens comprising of a total of 2 agents that were approved for the initial treatment of HIV.

(iii) The EMA Guideline on the clinical development of medicinal products for the treatment of HIV infection clearly outlined that the existing wording for the Tivicay indication was derived from the marketing authorisation holder having undertaken a study in patients with viral resistance relevant to the drug class of the agent being authorised. In other words, ViiV was able to obtain the aforementioned indication for Tivicay on the basis of the results of the VIKING-3 study, which investigated a completely different paradigm to the use of dolutegravir in combination with one other ARV in HIV treatment naïve patients. Specifically, VIKING-3 involved a double (bid) dose of Tivicay, and investigated this in combination with multiple other ARVs, in patients with a history of virological failure and resistance to the 'first generation' integrase inhibitors raltegravir and elvitegravir. Therefore, ViiV's argument that it was in accordance with the marketing authorization, and consistent with the Tivicay SPC, to promote new and unique combinations of DTG with just one other antiretroviral agent, that at the time of granting of the initial indication had not been assessed by EMA's Committee for Medicinal Products for Human Use (CHMP), was simply not correct.

Gilead stated that during the course of its follow up complaint, the Tivicay label was updated on 16 November to incorporate reference to the GEMINI studies. ViiV subsequently argued that as Sections 4.1 and 4.2 of the Tivicay SPC were not modified, this supported that the promotion of Tivicay in combination with 3TC during the Glasgow conference was appropriate. However, Gilead maintained that considering the nature of wording of the pre-existing indication available in the Tivicay SPC, clearly granted to ViiV on the basis of the results from the VIKING-3 study, the lack of change in Section 4.1 or 4.2 in itself did not validate ViiV's pre-license promotion of Tivicay with 3TC as a complete regimen for the treatment of HIV infection. In further support of the inappropriate interpretation of this indication by ViiV, Gilead noted that a new warning appeared in Section 4.4 of the Tivicay SPC following the Tivicay label update to incorporate the GEMINI data:

> **Lamivudine and dolutegravir**
> The two-drug regimen of dolutegravir 50 mg once daily and lamivudine 300 mg once daily was explored in two large randomized and blinded studies, GEMINI 1 and GEMINI 2 (see section 5.1). This regimen is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine.

Gilead stated that this emphatically supported that the combination of Tivicay with lamivudine (3TC) as a complete regimen was not considered to be within the previous scope of the marketing authorisation at the time of the Glasgow HIV conference and that the promotion of the use of Tivicay in combination with only 3TC as a complete regimen was not consistent with the Tivicay SPC at the time. The inclusion of the warning in Section 4.4 of the SPC confirmed that in the opinion of the CHMP there was important safety information which prescribers needed to be aware of when contemplating treatment with a regimen of Tivicay with 3TC. The promotion of this combination before the CHMP had finalized its consideration of the label update and before knowledge of, and without, the important safety information that in the opinion of the CHMP needed to be provided to prescribers created the exact harm that Clause 3.2 was aimed at preventing.

Gilead stated that whilst ViiV acknowledged that Section 4.4 of the Tivicay SPC was updated following the Type 2 variation to include the GEMINI data, it argued that the promotional material in question included the study eligibility criterion which was subsequently added to Section 4.4, and therefore the target audience would have been fully aware of the study population of which the results were predicated. However, Gilead did not accept this defence. According to the EMA, the objective of Section 4.4 of the SPC was to provide information on a specific risk when health professionals had to be warned of this risk or the risk led to a precaution for use to avoid harm. Associated warnings should be clear, compelling and effective. Clearly, simply sharing the inclusion criteria of a study from a single Phase 3 program did not replace the absence of this warning being available in the Tivicay SPC during its promotion with 3TC during the Glasgow HIV Conference. The warning was absent at this stage, of course, as the promotion took place before the CHMP had approved the update to the Tivicay marketing authorization to include the GEMINI data and agreed the associated warning now included in the updated SPC. It was a fundamental principle of the Code that the prescribing information was provided in a clear and legible manner in all promotional material (Clause 4.1), including reference to any warnings issued by the licensing authority (Clause 4.2) so that prescribers had all the relevant information needed about the products promoted to them to inform their prescribing

decisions, and within the correct context.
In summary, Gilead alleged that the promotion of the combination of Tivicay with 3TC as a complete regimen by ViiV during the conference was not in accordance with the marketing authorization for Tivicay at the time, was inconsistent with the SPC for Tivicay at the time and was therefore in breach of Clause 3.2 of the Code. Given the serious nature of the matter Gilead further alleged breaches of Clauses 2 and 9.1.

RESPONSE

ViiV submitted that its commercial stand did promote the use of Tivicay in combination with lamivudine at the HIV Drug Therapy 2018 Conference in October 2018 based on the results of the GEMINI studies. However, contrary to the assertion of Gilead, this promotion was not inconsistent with the marketing authorisation at the time. ViiV denied breaches of Clauses 3.2, 9.1 and 2.

ViiV submitted that the indication for Tivicay did not mandate a minimum number of ARVs to be included in combination therapies.

In October 2018 at the time of the promotion, Section 4.1 (Therapeutic Indications) of the SPC for Tivicay read:

> 'Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children above 6 years of age.'

ViiV submitted that this broad indication was based on a wide-ranging clinical study programme incorporating treatment naïve patients, those with resistance and those with very limited options. The indication aligned to the EMA guidance for the development of medicinal products for HIV infection. The EPAR (European Public Assessment Report) stated:

> 'Dolutegravir has demonstrated its efficacy in large scale studies covering previously untreated patients as well as those with advanced treatment histories and multi class resistance. In particular, a high barrier to resistance was demonstrated in the absence of integrase inhibitor class resistance.'

ViiV submitted that the indication wording was agreed with the EMA based upon these results and in line with the EMA's guideline on the content of the SPC, the indication for Tivicay listed the target disease as HIV, that it was for treatment (rather than eg cure) and included the age range. Other than the age range, the SPC did not restrict the patient population but it did include a restriction on how Tivicay should be used *('in combination with other anti-retroviral medicinal products')*. It did not specify which antiretroviral medicinal products or how many of them Tivicay must be combined with. This ensured that dolutegravir was not given as monotherapy rather than to ensure it was given with a specific number or types of other medicines.

Section 4.2 of the Tivicay SPC restricted prescription to clinicians experienced in the management of HIV. The indication therefore allowed experts the flexibility to use Tivicay at all stages of the disease and to adjust regimens to suit clinical need in individual cases where there may be tolerability or resistance issues.

In 2018 ViiV applied to update the marketing authorisation for Tivicay with the data from the GEMINI studies. This resulted in changes to the SPC and in particular to Section 5.1 (Pharmacodynamic Properties) and Section 4.4 (Special Warnings and Precautions for Use). There was no change to Section 4.1 (Therapeutic Indications) or Section 4.2 (Posology). The changes to the SPC came into effect on 15 November 2018.

ViiV submitted that regulations required only that promotion was not inconsistent with the marketing authorisation, not that promotion could only rely on data within the SPC.

Within its complaint, Gilead described in some detail the studies listed in Section 5.1 of the Tivicay SPC at the time of the conference in question. All of the studies listed featured use of Tivicay in combination with two or more ARVs and ViiV readily acknowledged that fact.

ViiV submitted that where it differed with Gilead was in Gilead's belief that the therapeutic indication of a medicine can only be promoted in the strict context of the studies that were mentioned in Section 5.1.

Clause 3.2 of the Code stated that promotion 'must not be inconsistent with the particulars listed in the summary of product characteristics.' It did not state that the studies being used to support promotion must be in the SPC. This was in line with the Medicines and Healthcare products Regulatory Agency (MHRA) position as stated in the Blue Guide:

> 'An advertisement may include statements not included in the SPC provided these can be substantiated and are not inconsistent with the SPC information'.

ViiV submitted that in the GEMINI studies, the regimen of Tivicay and lamivudine was used for the treatment of HIV in adults. This fitted squarely within the elements of the indication, namely, the treatment of HIV as part of combination therapy in adults. Accordingly, ViiV submitted that use of Tivicay with lamivudine as a complete regimen for the treatment of HIV did not violate Clause 3.2 of the Code. Moreover, there was nothing in the Tivicay SPC at the time that precluded its use with one other antiretroviral. The indication allowed for combined treatment and there were no contraindications or special warnings and precautions regarding the use of Tivicay in two drug regimens. ViiV maintained that the claims it made in October 2018, related to the GEMINI data, were not inconsistent with the relevant particulars of the SPC at the time.

ViiV submitted that following the update to the SPC for Tivicay in November 2018 Sections 4.1 (Therapeutic Indications) and 4.2 (Posology) remained unchanged. As the GEMINI data provided new information for health professionals it was

submitted for inclusion within the Tivicay label. When the Tivicay SPC was updated with the GEMINI data, no changes were made to the therapeutic indication or posology for Tivicay in Sections 4.1 and 4.2 of the SPC.

The SPC Guidelines from the EMA, and referred to by Gilead, made it clear that updates to Section 5.1 (Pharmacodynamic properties) of the SPC could only take place if they were consistent with the indication as described in Section 4.1 as follows:

> 'Where results from subsequent studies provide further definition or information on an authorised indication, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1.'

ViiV submitted that the fact that Section 5.1 was updated to include the results of the GEMINI studies supported ViiV's position that the use of Tivicay and lamivudine was consistent with the marketing authorisation. Finally, the fact that Section 4.4 of the SPC was updated in connection with the Type 2 variation did not retroactively make ViiV's use of the GEMINI data inappropriate. The need to exercise care in treating people living with HIV with resistance was well-known to physicians and the inclusion criteria for the GEMINI studies were communicated clearly within the stand materials.

ViiV submitted that it was responsible and appropriate that companies were allowed to inform health professionals of important updates to the safety or efficacy of a medicine within its licensed indication prior to an update to the SPC.

The SPC was a living document. It was updated throughout the life of a product to ensure it provided relevant current information to health professionals. However, there would be an inevitable time lag between new data being available and it being incorporated in to the SPC. During that period, sharing important information with prescribers was reasonable as long as the data being incorporated was not inconsistent with the information in the SPC. Common examples would be new drug interactions or additional side effects that might come to light during use of the medicine within its licensed indication. ViiV therefore refuted all allegations of breaches of Clause 3.2, 9.1 and 2.

ViiV noted Gilead's submission that the update to Section 4.4 (Special warnings and precautions for use) of the Tivicay SPC which resulted from the variation supported a view that promotion of the combination in October was outside the terms of the marketing authorisation. ViiV disagreed; its view was that it had significant new information about in-licence use of Tivicay available from the GEMINI studies and it was reasonable to communicate this to expert HIV physicians attending the international congress given that it was not inconsistent with information in the SPC at the time but only added to it. The wording that entered Section 4.4 of the SPC for Tivicay in November 2018 based on the GEMINI studies was as follows:

> **'Lamivudine and dolutegravir**
> The two-drug regimen of dolutegravir 50 mg once daily and lamivudine 300 mg once daily was explored in two large randomized and blinded studies, GEMINI 1 and GEMINI 2 (see section 5.1). This regimen is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine.'

ViiV submitted that at the time of the October conference the final wording, that would enter the SPC as a result of the variation, was not approved. As acknowledged by Gilead the information that the study populations consisted only of those with, 'no major RAMS [resistance associated mutations]' was included clearly in the congress stand materials, and as such promoted the rational use of medicines and did not put patients at risk. The actual language on the stand could be considered to be more restrictive than the update to the wording in Section 4.4 of the SPC as it covered all major resistance mutations to any class of HIV medicine. The eventual wording in Section 4.4 restricted only with known or suspected resistance to integrase inhibitors and lamivudine. Other entry criteria such as a baseline screening RNA of <500,000 copies per ml were also stated on materials.

ViiV noted that as pointed out by Gilead, prescribing information must also include 'any warning issued by the Medicines Commission, the Commission on Human Medicines, the Committee on Safety of Medicines or the licensing authority' but they did not include the rest of the sentence which stated 'which is required to be included in advertisements'. There were no specific warnings in the Tivicay SPC that the licensing authority had required to be included in advertisements either at the time of the conference or currently.

ViiV submitted that it was unsure as to whether Gilead was alleging breaches of Clauses 4.1 and 4.2. For clarity, the prescribing information for Tivicay that was current at the time of the congress was freely available during promotional activities. Clearly it could not, at that time, contain the new safety or efficacy information related to combination use with lamivudine as the SPC was yet to be updated. ViiV therefore denied a breach of Clause 4.1 or 4.2 if alleged.

PANEL RULING

The Panel noted Gilead's allegation that ViiV had promoted Tivicay (dolutegravir (DTG)) outside the terms of its marketing authorization at a conference in October 2018 by promoting the GEMINI-1 and GEMINI-2 studies which evaluated DTG in combination with just one other anti-retroviral agent, lamivudine (3TC), together with various accompanying claims. Gilead did not refer to specific materials but provided photographs of exhibition stand panels which it stated were 'some examples'. The Panel therefore considered the allegation in general and not in the context of any specific materials at the conference in question. The Panel noted that Clause 3.2 of the Code stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with

the particulars listed in its summary of product characteristics (SPC).

The Panel noted that the indication in Section 4.1 of the Tivicay SPC stated:

> 'Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children above 6 years of age'.

The Panel noted that the indication in Section 4.1 did not specify a minimum or a maximum number of ARV medicines that Tivicay should be combined with. Section 4.2 (posology and method of administration) stated that Tivicay should be prescribed by physicians experienced in the management of HIV infection. Section 5.1 (pharmacodynamic properties) referred to various combinations of DTG with other ARV medicines including 3TC.

The Panel noted Gilead's assertation that at the time Tivicay was granted a marketing authorization for the above indication, no data existed on the use of DTG in combination with one other ARV agent in HIV treatment naïve patients. ViiV acknowledged that all the studies listed in Section 5.1 of the Tivicay SPC at the time of the conference featured use of DTG in combination with two or more ARV agents.

The Panel noted that at the time of the conference, the Tivicay SPC did not refer to the GEMINI studies. According to ViiV, following the conference, in November 2018, the SPC was updated to include, *inter alia*, GEMINI-1 and GEMINI-2 study results in Section 5.1 and information based on these studies was included in Section 4.4 (special warnings and precautions for use) which stated:

> **'Lamivudine and dolutegravir**
> The two-drug regimen of dolutegravir 50 mg once daily and lamivudine 300 mg once daily was explored in two large randomized and blinded studies, GEMINI 1 and GEMINI 2 (see section 5.1). This regimen is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine'.

The Panel noted Gilead's assertation that the update to Section 4.4 of the Tivicay SPC supported the company's view that the combination of Tivicay with lamivudine as a complete regimen was not considered to be within the scope of the marketing authorization at the time of the conference and that this SPC update constituted important safety information which prescribers needed to be aware of when considering a regimen of Tivicay plus lamivudine.

The Panel noted ViiV's submission that the information regarding the GEMINI studies on the exhibition stand at the conference could be considered more restrictive than the subsequent SPC update to Section 4.4 as it covered the exclusion of patients with all major resistance mutations to any class of HIV medicine and referred to other study entry criteria such as a baseline screening RNA of <500,000 copies per ml.

The Panel further noted ViiV's submission that when the SPC was updated with the GEMINI studies, no changes were made to Section 4.1 (therapeutic indications) or Section 4.2 of the SPC.

In the Panel's view it was not necessarily unacceptable to promote a medicine using studies that were not listed in its SPC as long as such data was not inconsistent with the particulars listed in the SPC. In the Panel's view, using Tivicay in combination with one other ARV medicine in HIV was not in itself inconsistent with the indication for Tivicay to be used in combination. Physicians might decide not to use a two drug-regimen prior to the availability of data.

The Panel noted its comments above and considered that Gilead had not proved, on the balance of probabilities, that ViiV's promotion of Tivicay in combination with lamivudine at the October 2018 conference in general, constituted promotion of Tivicay outside the terms of its marketing authorization or in a manner that was inconsistent with its SPC. No breach of Clause 3.2 of the Code was ruled. The Panel noted that any allegations in relation to specific materials would be considered on their own particular merits.

The Panel did not consider that ViiV had failed to maintain high standards and ruled no breach of Clause 9.1.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted its rulings of no breach above and consequently ruled no breach of Clause 2.

2 Alleged use of Tivicay data in combination with two antiretroviral agents to support promotion of Tivicay with one antiretroviral agent

COMPLAINT

(i) General use of data on dolutegravir (DTG) combined with two antiretroviral agents to support promotion of DTG with one antiretroviral agent, including the claim 'Only dolutegravir has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens' [UK/DTGRPV/0033/18(3)]

Gilead stated, as background, since 1996, in patients without virological resistance, the foundation of HIV management had been built upon the use of 3 antiretroviral agents, comprising of 2 NRTIs and a third agent (together known as Highly Active Antiretroviral Therapy [HAART], or triple therapy). To this day, all major international HIV guidelines still preferentially recommended regimens with 3 active antiretroviral agents based on 2 NRTIs and a third agent for the initial treatment of HIV.

Gilead stated that the integrase inhibitor, dolutegravir, had been investigated as the third agent using this triple therapy paradigm in several treatment naïve studies (SINGLE, SPRING-2,

FLAMINGO), which contributed to the initial (or early) Tivicay marketing authorization. In two of these studies (SINGLE, FLAMINGO), dolutegravir combined with 2 NRTIs (ie DTG-based triple therapy) demonstrated statistically superior efficacy versus comparator (when also combined with 2 NRTIs) in an intent-to-treat analysis at the 48 week primary endpoint. In addition, in the SAILING study, dolutegravir taken once daily in combination with an investigator selected background regimen consisting of up to 2 agents (including at least one fully active agent) in patients with prior treatment failure, but not exposed to the integrase class, dolutegravir was found to have statistically superior efficacy in an intent-to-treat analysis versus comparator at the primary endpoint. In the SAILING study, 71% of patients had at least 2 active agents as background in addition to dolutegravir, and at least 64% of patients were also administered a ritonavir-boosted protease inhibitor (PI/r).

Gilead stated that as a consequence of the results of the SINGLE, SPRING-2 and FLAMINGO studies, dolutegravir was preferentially recommended in all major international HIV guidelines in combination with various NRTI backbones (ie in a combination with 2 NRTIs to form a DTG-based triple therapy) for the initial treatment of HIV.

Gilead stated that more recently, dolutegravir had been studied in combination with rilpivirine in the SWORD study (ie studied as a DTG based 2-drug regimen or DTG-based dual therapy). In the SWORD study, HIV-1 infected adults who were virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor were randomized to remain on their baseline regimen or switch to a combination of dolutegravir and rilpivirine. The limited nature of this population was reflected in the Juluca (dolutegravir/rilpivirine) SPC indication. In this study, the switch to dolutegravir/rilpivirine demonstrated non-inferior efficacy versus remaining on background regimen over 48 weeks in these participants with HIV suppression at baseline.

In addition, dolutegravir had recently been studied in combination with 3TC in participants (≥18 years) with HIV-1 infection and a screening HIV-1 RNA of 500,000 copies per mL or less, and who were naive to antiretroviral therapy (the GEMINI study). At week 48, in the pooled GEMINI intention-to -treat-exposed population, non-inferior efficacy was demonstrated with dolutegravir and 3TC compared with once-daily dolutegravir plus 2 NRTIs.

Gilead stated that a review of the above studies demonstrated that the SWORD and GEMINI studies differed substantially from the SINGLE, SPRING-2, FLAMINGO and SAILING studies on multiple important aspects:

- SINGLE, SPRING-2, FLAMINGO involved the use of dolutegravir in combination with 2 other antiretroviral agents (2 NRTIs), whereas SWORD and GEMINI each involved the use of dolutegravir in combination with 1 other antiretroviral agent. In SWORD, dolutegravir was combined with rilpivirine, an NNRTI, whereas in GEMINI, dolutegravir was combined with 3TC, an NRTI. In both the SWORD and GEMINI studies, the combinations of DTG plus rilpivirine and DTG plus 3TC were respectively considered investigational regimens, tested against standard of care triple therapy.
- The SINGLE, SPRING-2, FLAMINGO studies did not specify an upper limit on baseline HIV-1 RNA viral load at study entry. In contrast, the GEMINI study required that treatment naïve patients had a baseline screening HIV-1 RNA of 500,000 copies per mL or less. In the field of HIV, there were multiple examples where certain ART combinations had performed less favourably in patients with higher baseline viral load, and in many cases this feature has heavily influenced how guidelines committees viewed the utility of various HIV regimens, as reflected by their positioning within HIV treatment guidelines.
- The SWORD study was restricted to HIV-1 infected adults who at baseline were virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor. As already mentioned, the specificity of this population was reflected in the indication of the dolutegravir/rilpivirine (Juluca) SPC.
- The SAILING study involved the use of dolutegravir taken once daily in combination with an investigator selected background regimen consisting of up to 2 agents (including at least one fully active agent) in patients with prior treatment failure, but not exposed to the integrase class. 71% of patients had at least 2 active agents as background in addition to dolutegravir, and at least 64% of patients were also administered a ritonavir-boosted protease inhibitor (PI/r). This was clearly a different population to those who were studied in GEMINI or SWORD, considering patient baseline characteristics, clinical history, and the number and nature of ARVs used across these studies.

Gilead stated that despite the important differences described in the various studies above, in the context of promotion of Juluca and Tivicay plus 3TC, ViiV had developed material which made claims about data on DTG with two antiretroviral agents (DTG-based triple therapy) to support promotion of DTG with one antiretroviral agent (DTG-based dual therapy). Gilead alleged that use of data in this fashion breached Clauses 7.2, 7.3, 7.4 and 9.1 of the Code.

Item UK/DTGRPV/0033/18(3)-'Only dolutegravir has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens'

Gilead stated that the above claim appeared in the context of the promotion of Tivicay + 3TC (item UK/DTGRPV/0033/18(3) available on the UK ViiV Exchange website (https://uk.viivexchange.com/our-medicines/2dr/). Gilead alleged that this claim when used in the context of the promotion of two drug regimens was in breach of Clauses 7.2 and 7.4 of the Code.

The claim 'Only dolutegravir has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens' was used to support the overarching question 'What makes DTG an ideal core agent to power a 2DR?'. This gave the clear misleading impression that results with DTG based 3 drug regimens might also be applied when DTG was given as part of a 2 drug regimen, especially when considering the relative prominence of '2DR' in the title, compared with '3-drug regimen' in the smaller copy, and the clear promotional focus of item UK/DTGRPV/0033/18(3) toward DTG-based 2 drug regimens. Furthermore, throughout the course of intercompany dialogue, ViiV had not been able to substantiate that the results observed in either the GEMINI or SWORD studies were because of any efficacy data that were generated with DTG when given as part of a 3 drug regimen, and as such ViiV had not been able to substantiate the impression given by the use of this claim in the two drug regimen context.

Gilead stated that during inter-company dialogue, ViiV had stated that the claim 'Only dolutegravir has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens' made it immediately clear to readers that it related to 3 drug regimens only and was therefore unambiguous, and also stated that previous 2 drug regimens had shown variable efficacy, and therefore it was important to contextualise why a DTG based 2 drug regimen was different to previous 2 drug regimens. For the reasons indicated above, Gilead did not accept that including the words 'as part of a 3 drug regimen' removed the misleading impression that the superior efficacy would also be seen with the two drug regimens being promoted. In addition, to state that 'it is important to contextualise why a DTG based 2 drug regimen is different from previous 2 drug regimens' was in itself incapable of substantiation as there was no available data directly comparing DTG based 2 drug regimens with 2 drug regimens that did not contain DTG. While ViiV correctly stated that previous 2 drug regimens had shown variable efficacy, there was no direct evidence in the literature to support that 2 drug regimens that had demonstrated lower efficacy in clinical trials were expected to do so based on their performance as part of 3 drug regimens. In summary, Gilead asserted that the only claim that should be made regarding promoted regimens or combinations - in this case Tivicay and 3TC, or Juluca should be restricted to the evidence that had been generated with those specific regimens. Gilead alleged that failure to do so was a breach of Clauses 7.2, 7.3 and 7.4 of the Code. Gilead did not consider that high standards had been maintained and alleged a breach of Clause 9.1.

(ii) 'Unbeaten in head to head clinical trials'

Gilead stated that the claim 'Unbeaten in head to head clinical trials' was also made at the ViiV stand during the Glasgow HIV Conference. Despite Gilead's request to have this claim removed during a face to face discussion with ViiV on 29 October, it remained on display during the entire course of the conference.
Gilead stated that during the course of inter-company dialogue, it highlighted multiple issues associated with this claim, namely:

- That health professionals were required to click through on the main display in order to understand the basis of the claim was alleged to be in breach of Clause 7.2 in that the claim was ambiguous and not capable of standing alone. This main display was clearly visible to all conference delegates in a high traffic area, with only a nominal percentage likely pausing to click through to review the material in its entirety. Through the course of intercompany dialogue, ViiV stated that there was no requirement for the reader to 'click through' to understand the statement 'unbeaten in head to head clinical trials', however this did not appear to be the case. The page in question was prominent and required the reader to 'tap' to explore the dolutegravir (DTG) data. Thus, without audience interactivity, this page was essentially all the audience would read, and therefore any relevant claims must clearly and prominently be capable of being substantiated from the information within this page. This was not the case.
- The evidence used to support this claim (not visible on the main initial panel) was from 10 clinical trials of DTG in various combinations and populations and 4 clinical trials when used as a two-drug regimen. A review of all the content at the ViiV stand showed a clear promotional focus on DTG in combination with either rilpivirine or 3TC. Consequently, similar to Point 2 (i) above, Gilead alleged that the use of data derived from DTG-based triple therapy studies to support this claim in the context of DTG-based dual therapy promotion was ambiguous, misleading and gave the impression that the attributes of dolutegravir seen in the triple therapy studies were also delivered when dolutegravir was used as part of a two drug regimen. Gilead alleged that this was in breach of Clauses 7.2, 7.4, and 9.1 of the Code
- The claim 'unbeaten' was in itself misleading, ambiguous, and did not compare medicines for the same needs or intended for the same purpose and was therefore alleged to be in breach of Clauses 7.2, 7.3, 7.4 and 9.1 of the Code. ViiV stated that 'unbeaten' was defined by the Oxford Dictionary as meaning 'not surpassed or undefeated'. However, this definition clearly did not exclude the potential that the promoted regimens might have actually surpassed or defeated the comparator in some instances, thus highlighting the ambiguity of the claim. While this ambiguity was exacerbated by the fact that ViiV had used data on DTG-based triple therapy to support the claim (which had surpassed comparator in the measure of efficacy in some instances), the fact that DTG-based 2 drug regimens had never surpassed comparator in any clinical studies (Gilead speculated for the measure of efficacy), also rendered the claim misleading. Even if taking a more conservative approach, where a reader might interpret the claim as meaning 'has not been beaten' and restricted to studies that included DTG-based 2 drug regimens, the claim was still an overstatement as the piece in question did not adequately specify the restricted populations in which Juluca or Tivicay + 3TC were studied, in the SWORD and GEMINI studies respectively.

Instead, it gave the misleading impression that the promoted combinations were unbeaten across all populations in which triple therapies had been studied. While Gilead did not expect that a specific regimen was required to be studied against every possible combination or permutation of HIV medicines in order to be able to potentially make these types of all-encompassing claims, in this particular case there were some clear exclusion criteria for each of the SWORD and GEMINI studies that must be clearly made prominent if considering making any claims versus standard of care regimens; specifically, in SWORD (Juluca), patients were required to be virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor, whereas in GEMINI (Tivicay plus 3TC), patients were excluded if their baseline HIV-1 RNA exceeded 500,000 copies/ml, and patients with genotypic resistance to any class of drugs were excluded (as opposed to just within the drug classes being studied). These types of restrictions did not apply to standard of care triple therapy.

- In addition, as already raised in Point 1, Gilead alleged that any proactive discussion of the use of Tivicay + 3TC during the Glasgow conference was in breach of Clause 3.2 of the Code and Gilead did not accept that any references citing this combination should have been used to support this or any claim during the Glasgow conference.

RESPONSE

ViiV did not accept that it was in breach of the Code in respect of any of the allegations made by Gilead.

(i) General use of data on dolutegravir combined with two antiretroviral agents to support promotion of dolutegravir with one antiretroviral agent

ViiV stated that Gilead had gone to some lengths in its complaint to point out the differences between the various studies involving dolutegravir in combination with other ARVs. In particular, they had highlighted the differences between the studies involving dolutegravir in a three-drug regimen and those where it was a part of a two-drug regimen and alleged 'that use of data in this fashion breaches Clauses 7.2, 7.3, 7.4 and 9.1'. However, Gilead did not make clear exactly in what way each of those clauses were breached. As ViiV understood it, the complainant had the burden of proof with respect to how the use of the data was misleading (Clause 7.2), in what way a comparison was inappropriate (Clause 7.3), how the information was not capable of substantiation (Clause 7.4) and in what way high standards had not been maintained (Clause 9.1).

Tivicay was indicated in combination with other antiretrovirals as a treatment for HIV and ViiV promoted its use in both three and two drug regimens as new data continued to be produced. ViiV submitted that treatments for HIV infection, although highly effective in suppressing viral replication, had the potential for significant side effects. Thus, whilst therapy with three ARVs had been the mainstay of treatment for most patients, clinicians and researchers had naturally questioned whether two-drug regimens could work equally well. Unfortunately, when two-drug regimens were first studied, although better than monotherapy, they had limited efficacy because only one class of drug (NRTI) was available at the time. This meant that the HIV virus was attacked at only one point in its lifecycle and resistance to treatment could develop more readily. It was not until the introduction of new classes of ARVs, which when used in combination could target the virus in two different ways, that HIV therapy became substantially more effective. This two-pronged approach to the virus lifecycle had been the mainstay of HIV treatment and was recommended in all major treatment guidelines. For most people this involved taking a three-drug ARV regimen.

ViiV submitted that since its introduction, dolutegravir had become integral to guideline recommended three-drug ARV regimens for a wide range of patients. In combination it had shown superiority over comparators in a number of three-drug regimens, and resistance had only rarely been observed both in clinical trials and real-world settings. In every phase 3, head to head study that dolutegravir had been included in, the results had either shown dolutegravir based regimens to be superior or non-inferior in comparison with regimens based on other ARVs. No combination of ARVs had shown superiority over a dolutegravir based regimen in any head-to-head clinical trial in any patient population. It was this history that the materials conveyed as context to the promotion of dolutegravir based two-drug regimens. It was to reassure the prescriber that two-drug regimens based on dolutegravir were not the same as historical two-drug regimens.

ViiV submitted that it was not suggesting, as Gilead implied, that the superior efficacy results observed in studies in some dolutegravir based three-drug regimens could be extrapolated directly to its use in two-drug regimens. ViiV was clear in all cases that the results from the GEMINI studies showed non-inferiority. Importantly the comparator arm in the GEMINI studies was also a dolutegravir-based three drug regimen (DTG+ tenofovir disoproxil fumarate and emtricitabine TDF/FTC). The inclusion of three drug regimen dolutegravir data provided context about the 'gold standard' nature of the comparator arm and thus provided reassurance. It was also clear to the readers (expert HIV physicians) which studies were using 3 drug regimens and which were using two drug regimens.

ViiV rejected the assertion by Gilead that providing context around dolutegravir based therapies was ambiguous or misleading in breach of Clause 7.2. ViiV also rejected the alleged breach of Clause 7.3 and was unsure in what way an unfair comparison was being made and with respect to what medicines.

ViiV submitted that its materials were clear that DTG+3TC and JULUCA were non-inferior. Its claims with respect to use of dolutegravir in two-drug or three-drug regimens were substantiated fully by the study data quoted and consequently it rejected a breach of Clause 7.4.

ViiV submitted that information regarding the use of dolutegravir in three-drug regimens was both fully substantiated and justified to provide context to the use of dolutegravir in two-drug regimens and that it had maintained high standards in communicating this. ViiV denied a breach of Clause 9.1.

'Only dolutegravir has shown superior efficacy vs 5 different ART comparators when evaluated as part of a 3-drug regimen' – Item VIIV/DTGRPV/0033/18(3)

ViiV noted Gilead's allegation that use of the statement above, in response to a question in the item asking why dolutegravir was chosen as the 'core agent' in a two-drug regimen in some way implied that the superior efficacy observed in three-drug regimen studies could be applied to the two-drug regimen of dolutegravir and lamivudine. ViiV rejected this interpretation. The reader was left in no doubt that the claim was related to use of dolutegravir as part of a three-drug regimen as it was clearly stated as such within the claim itself. It was impossible to see how a specialist in the management of HIV would, from that statement, assume that dolutegravir had shown superior efficacy versus comparators when used as part of a two-drug regimen. The claim was unambiguous and fully substantiated by the references used; ViiV denied breaches of Clauses 7.2 and 7.4. No comparisons were being made except between dolutegravir based regimens and the comparator regimens mentioned in the claim and those were all fully referenced and substantiated. ViiV therefore denied a breach of Clause 7.3. ViiV had maintained high standards in its communication about the use of dolutegravir as a basis for a two-drug regimen and therefore it denied a breach of Clause 9.1.

(ii) 'Unbeaten in head-to-head clinical trials' – Claim used on the promotional booth at the HIV Drug Therapy 2018 Conference in Glasgow

ViiV submitted that the claim at issue was the headline to a screen on an interactive panel with a subheading inviting physicians to tap to explore dolutegravir data. The stand itself was fundamentally promoting Tivicay. Tivicay was indicated in combination with other anti-retroviral medicinal products for the treatment of HIV infected adults, adolescents and children above 6 years of age. As such it could be used with a number of different ARVs in all types of HIV patients. It was not contrary to the Code for a company to promote different ways of using its product as long as it was not inconsistent with the SPC and compliant with the Code.

Contrary to Gilead's assertion, the claim was capable of standing alone even without tapping on the data. In every single head to head trial that dolutegravir had been in, either as part of a 3 drug regimen or a 2 drug regimen, the results showed that it had always matched or surpassed its comparators and Gilead did not dispute this. A 2015 review of the pharmacology, efficacy and safety of dolutegravir stated that it was '… equivalent or superior to existing treatment regimens in both treatment-naïve and treatment-experienced patients including those with previous raltegravir or elvitegravir failure'. Studies in the intervening years continued to support this.

Whether those reading the claim tapped on the screen to find out more information or not, they were not misled about the clinical trial outcomes data for dolutegravir based therapy. The Code required that all information, claims and comparisons must be capable of substantiation but there was no requirement that the substantiation must appear on the same page.

Clause 7.5 made clear that 'Substantiation for any information, claim or comparison must be provided as soon as possible, and certainly within ten working days, at the request of members of the health professions or other relevant decision makers'. The claim could stand alone, was unambiguous, and fully capable of substantiation. ViiV therefore denied a breach of Clause 7.2.

ViiV noted that Gilead alleged breaches of Clauses 7.2, 7.4 and 9.1 in that the claim 'gives the impression that the attributes of dolutegravir seen in triple therapy are also delivered when dolutegravir is used as part of a two-drug regimen'. The claim was true whether one was considering dolutegravir in a two-drug or three-drug based regimen. ViiV was not suggesting that the superior efficacy results observed in some dolutegravir based three drug regimen studies could be extrapolated directly to its use in two-drug regimens. The claim, in common with the other claims at issue, conveyed the strength of the data with respect to dolutegravir based therapy, when dolutegravir was used in a manner consistent with its broad marketing authorisation. ViiV consequently believed the claim to be accurate and capable of substantiation and denied breaches of Clauses 7.2, 7.4 and 9.1.

With regard to the use of the word 'unbeaten', ViiV rejected Gilead's allegations and submitted it did not imply superiority and did not imply the studies were taking place in the same populations of patients. The word 'unbeaten' was simply stating that dolutegravir based therapy had in no instance been shown to be inferior to any comparator regimen across all the patient groups it has been tested. All those patient groups fell within the licensed indication for dolutegravir.

The screen in question contained no details of the patient populations in the studies that led to the claim, but the claim was nevertheless true and those wishing to understand the substantiating evidence could explore the data in detail. The screen made no reference to superiority and contained three buttons which allowed clinicians the opportunity to view the GEMINI data, the SWORD data or the depth and breadth of DTG clinical trial data.

With regard to Gilead's view that the claim 'unbeaten' in the sense of 'has not been beaten'

was 'an overstatement as the piece in question did not adequately specify the restricted populations in which Juluca or Tivicay + 3TC were studied in the SWORD and GEMINI studies respectively' and stated that these 'types of restrictions do not apply in standard of care triple therapy', ViiV submitted in response that all randomised controlled clinical trials had populations restricted in some way and this fact was entirely understood by health professionals.

Within the HIV therapy area it was inconceivable that an expert physician viewing this claim would assume that all the studies referred to identical patient populations.

There was no precedent by which claims based on a clinical trial must be explicitly accompanied with all inclusion and exclusion criteria from that trial. They must be accurate of themselves, not mislead and be based on study populations consistent with the marketing authorisation. All this was true for the claim 'Unbeaten in head-to-head studies' with respect to both two- and three-drug dolutegravir regimens.

ViiV noted Gilead's implication that some special case should be made in the case of dolutegravir two-drug regimen claims as the 'types of restrictions' in the SWORD and GEMINI studies did not apply in three-drug regimens. This, however, was patently not the case. The licences for several antiretrovirals including Gilead medicines used as three-drug therapy demonstrated restrictions which came about as a result of the entry criteria for clinical studies, for instance:

- Odefsey was indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV-1 RNA copies/mL
- Atripla was indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Atripla prior to initiation of their first antiretroviral treatment regimen
- Biktarvy was indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

ViiV submitted that the claim 'unbeaten in head-to-head clinical trials' in respect of dolutegravir based therapy was consistent with the evidence for all two- and three-drug dolutegravir based therapies and it was not making a comparison. ViiV denied a breach of Clauses 7.2, 7.3, 7.4 and 9.1.

PANEL RULING

(i) General use of data on DTG combined with two antiretroviral agents to support promotion of DTG with one antiretroviral agent

The Panel noted that item VIIV/DTGRPV/0033/18(3) was a webpage on the ViiV exchange website with a focus on 2-drug regimens. The webpage included the subheading 'What makes DTG an ideal core agent to power a 2DR [2-drug regimen]?'. Below this, in smaller font, it stated 'Only dolutegravir…' followed by a number of claims including: 'Has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens'; and 'Is PROVEN EFFECTIVE in 2-drug regimens with lamivudine in treatment-naïve adult patients at 48 weeks and rilpivirine in virologically suppressed patients at 100 weeks'. 'SUPERIOR EFFICACY' and 'PROVEN EFFECTIVE' in the above two claims were in a different coloured font to the surrounding text.

The Panel noted that below this section of the webpage was a 'learn more' section which stated 'Explore dolutegravir-based, 2-drug regimens for your diverse patient needs' followed by the logos for Tivicay + lamivudine and Juluca.

The Panel noted Gilead's allegation that the claim in question 'Only dolutegravir…Has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens' in the context of the promotion of two-drug regimens gave the misleading impression that results with DTG-based three-drug regimens might also be applied when DTG was given as part of a 2-drug regimen considering the relative prominence of '2DR' in the title compared with '3-drug regimens' in the smaller font and the promotional focus of the webpage on 2-drug regimens.

The Panel noted ViiV's submission that the claim in question was not suggesting that the superior efficacy results observed in some DTG based 3-drug regimen studies could be extrapolated directly to its use in 2-drug regimens and that the claim was related to use of DTG as part of a three-drug regimen which was clearly stated and substantiated by the references.

The Panel noted that both the Tivicay and the Juluca SPCs stated that these medicines should be prescribed by physicians experienced in the management of HIV infection. The Panel considered the immediate and overall impression to an HIV physician. In the Panel's view, although the claim in question featured on a webpage promoting DTG-based 2-drug regimens, it appeared beneath the question of what made DTG an ideal core agent to power a 2-drug regimen. In the Panel's view it was clear that 'SUPERIOR EFFICACY' in the claim 'Only dolutegravir…Has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens' was in relation to DTG as a core agent in a 3-drug regimen and not in relation to a 2-drug regimen as alleged. An associated claim stated that DTG was '…PROVEN EFFECTIVE…' in two specific 2-drug regimens in certain patients. In this regard, the Panel considered that the intended

audience would not be misled as alleged. Gilead had not shown, on the balance of probabilities, that the claim 'Only dolutegravir…Has shown SUPERIOR EFFICACY vs 5 different ART comparators when evaluated as part of a 3-drug regimens' was misleading or incapable of substantiation and the Panel therefore ruled no breach of Clauses 7.2, 7.3 and 7.4.

The Panel did not consider that ViiV had failed to maintain high standards in this regard and ruled no breach of Clause 9.1.

(ii) 'Unbeaten in head to head clinical trials'

The Panel noted that the claim at issue appeared on an interactive stand panel at the ViiV stand at the HIV Drug Therapy 2018 conference, as referred to above at Point 1.

The stand panel was headed 'Unbeaten in head to head clinical trials' and directly below, in smaller font, it stated 'Tap to explore the dolutegravir (DTG) data'. To the left of the heading was a circle that stated 'Powered by DTG at the core'. Below this were three large circles which were labelled: GEMINI-1 and GEMINI-2 data, SWORD-1 and SWORD-2 data, and depth and breadth of DTG clinical trials. When the circles were accessed, further information about the studies was provided, including that the GEMINI and SWORD studies were non-inferiority studies and evaluated DTG as part of a 2-drug regimen and that 10 studies, including superiority and non-inferiority studies, evaluated DTG as part of a 3-drug regimen.

That Panel considered that the first screen of the interactive stand panel needed to stand alone as not all individuals would stop to click through the screens and read the supporting information.

The Panel noted ViiV's submission that in every phase 3, head to head study that DTG had been included in, the results had either shown DTG based regimens to be superior or non-inferior in comparison with regimens based on other ARVs and that no combination of ARVs had shown superiority over a DTG-based regimen in any head-to-head clinical trial in any patient population.

In the Panel view, the word 'unbeaten' would imply to the audience that DTG was unsurpassed in any head-to head clinical trials and not necessarily that it had superior efficacy or had surpassed its comparators.

The Panel noted that the interactive screens on the stand panel predominantly referred to DTG-based 2-drug regimens which were evaluated in non-inferiority studies (SWORD-1, SWORD-2, GEMINI-1 and GEMINI-2). In the Panel's view, non-inferiority studies evaluated whether one treatment was non-inferior to another treatment by a pre-specified margin. In this regard, the Panel queried the use of 'unbeaten' in the claim given that the material predominantly referred to DTG-based 2-drug regimens which were only supported by non-inferiority studies. This was reinforced by the layout and reading left to right would mean viewing the non-inferiority data first. Context was important. The Panel considered that the claim on the stand panel in question which was immediately followed by 'Tap to explore the dolutegravir (DTG) data' encompassed all DTG clinical trials, including DTG-based 3-drug regimens which had been evaluated in both superiority and non-inferiority studies. The Panel therefore considered the body of evidence for the claim ie both 2-drug and 3-drug DTG based regimens noting that there were a number of studies.

The Panel noted that Gilead had provided no evidence to suggest that there were ARV combinations that had surpassed either a 2-drug or a 3-drug DTG-based regimen in any head-to-head clinical trial.

The Panel noted Gilead's assertation that the screen with the claim in question did not adequately specify the restricted populations in the SWORD and GEMINI studies. The Panel noted that the screen in question contained no details of the patient populations in the studies and a user would have to click on the screen to access such information. In the Panel's view, this was not necessarily unacceptable provided that the information on the screen in question was not misleading. The Panel noted that both the Tivicay and the Juluca SPCs stated that these medicines should be prescribed by physicians experienced in the management of HIV infection. The Panel noted ViiV's submission that it was inconceivable that an expert HIV physician viewing the claim would assume that all the studies referred to identical patient populations.

The Panel noted its comments above and considered that although the claim 'Unbeaten in head to head clinical trials' was a strong, broad claim, there appeared to be data to support it and the audience would not be misled. Gilead had not shown, on the balance of probabilities, that the claim on the stand panel in question was ambiguous, misleading or incapable of substantiation as alleged and the Panel therefore ruled no breach of Clauses 7.2, 7.3 and 7.4.

The Panel did not consider that ViiV had failed to maintain high standards in this regard and ruled no breach of Clause 9.1.

Complaint received **26 February 2019**

Case completed **16 September 2019**