

GILEAD SCIENCES v ViiV HEALTHCARE

Promotion of Juluca

Gilead Sciences Europe complained about the promotion of Juluca (dolutegravir/rilpivirine) by ViiV Healthcare. Juluca was a combination of two antiretroviral (ARV) medicines used in the treatment of human immune deficiency virus type-1 (HIV-1) infection in adults who were virologically-suppressed on a stable ARV regimen for at least 6 months. Gilead also marketed ARV combination medicines for the treatment of HIV.

The detailed response from ViiV is given below.

1 Reduction of antiretroviral (ARV) exposure and potential associated toxicities

Gilead complained about four similar statements within four different materials. Gilead stated that whilst each statement was slightly different, the following two claims were made in the context of the promotion of Juluca:

- (i) reducing the number of ARV medicines from [not stated] to two would reduce a patient's ARV exposure;
- (ii) this reduction translated into a reduction in potential associated toxicities.

Gilead alleged that these statements and claims were inaccurate, ambiguous, misleading, could not be substantiated and did not reflect the available evidence on adverse events.

The Panel considered each statement separately in the context of the material in which it appeared. The two allegations were ruled upon separately in each of the statements at issue.

A 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure & potential associated toxicities' (Juluca leavepiece (ref UK/DTGRP/0006/18))

The Panel noted that the statement at issue included 'streamline' and further noted that ViiV had agreed following inter-company dialogue to withdraw materials that used this term. The Panel therefore made no ruling with regard to the reference to 'streamline'.

The Panel noted that the claim at issue appeared as a heading on the back page of a 4 page bi-folded A5 leavepiece which appeared to the Panel to be the final page that a user would read.

The Panel understood that drug exposure was a defined term in clinical pharmacology and it could be affected by numerous factors. The Panel noted that the statement at issue was in relation to ARV

exposure and therefore encompassed all medicines within an ARV regimen. In the Panel's view, a reduction from a 3-medicine to a 2-medicine regimen reduced the number of ARV medicines that a patient was exposed to but it might not necessarily reduce the patient's ARV exposure as a measure of the concentration of ARV medicine in the body with respect to time; there were many factors to be considered, *inter alia*, dosage and interactions which could affect the clearance of one or more of the medicines in the regimen. Context and the audience were also important. The Panel noted that the statement at issue was below the caveat 'Based on the SWORD study results ...'. The Panel further noted ViiV's submission that the SWORD studies included multiple ARV combinations in the comparator arm. The Panel noted, however, that the Llibre *et al* publication did not discuss exposure in subjects switching from triple therapy to dolutegravir/rilpivirine in terms of quantitative measures of total systemic drug exposure such as area under the curve (AUC). The Panel considered that the claim in question 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure and potential associated toxicities' was such that some HIV physicians might consider that there was pharmacokinetic drug exposure data for dolutegravir/rilpivirine versus the different triple therapy combinations in, *inter alia*, the SWORD studies and that was not so.

The Panel noted its comments above. In the Panel's view, and on balance, treatment with a two-medicine regimen did not necessarily mean that there was a reduction in ARV exposure versus treatment with a three-medicine regimen. The properties of each medicine in the regimen were relevant to ARV exposure. In this regard, the Panel considered that the reference to a two-drug regimen reducing ARV exposure versus a three-drug regimen in the claim 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure & potential associated toxicities' was ambiguous, unsubstantiated and a misleading comparison. Breaches of the Code were ruled.

The Panel noted Gilead's allegation regarding the claim in the second half of the statement at issue which suggested that a reduction in ARV exposure reduced potential associated toxicities.

The Panel noted that the Llibre *et al* publication referred to adverse events, including a breakdown from grade 1 to 4. The Panel considered that the use of the term 'toxicity' was ambiguous in relation to the SWORD study results and it was unclear if it related to a particular grade or type of adverse event.

The Panel noted that the preceding page of the

leavepiece included the heading 'Juluca – reduce your patients' ARV exposure & potential associated toxicities' beneath which were claims regarding statistically significant recovery in bone mineral density and maintained lipid levels at 48 weeks. Within the same section of the leavepiece were statements related to adverse events, including rates of all adverse events, drug-related adverse events resulting in discontinuation and adverse events reported in >5% of subjects in the Juluca arm including psychiatric disorders, nasopharyngitis, headache and diarrhoea. The heading 'Juluca – reduce your patients' ARV exposure & potential associated toxicities', was separately subject to complaint at section B below; however, the Panel considered that this section of the leavepiece was relevant to the claim at issue on the back page (page 4). The Panel considered that the information on page 3 implied that the term 'toxicities' related to all types of adverse events and this implication was relevant to consideration of the claim in question on page 4.

The Panel noted that after switching to dolutegravir/rilpivirine, more subjects (77%) reported at least one adverse event by week 48 compared with subjects who continued with current ARVs (71%). Furthermore, adverse events stratified by grades 1 to 4 were either the same between the two treatment arms or higher with dolutegravir/rilpivirine.

The Panel noted that the statement at issue was below the caveat 'Based on the SWORD study results ...' and in the Panel's view the claim 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure and potential associated toxicities' with regard to reduction in potential associated toxicities could not be substantiated by the SWORD study results.

The Panel noted its comments above. In the Panel's view, the implication that a two-medicine regimen reduced potential associated toxicities versus a three-medicine regimen in the claim 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure & potential associated toxicities' was ambiguous, unsubstantiated, did not reflect the available information about adverse events and was a misleading comparison. Breaches of the Code were ruled.

B 'Juluca-reduce your patients' ARV exposure and potential associated toxicities' (Juluca leavepiece (ref UK/DTGRP/0006/18) and ViiV exchange website (ref UK/DTGRP/0034/18(1))

Juluca leavepiece (ref UK/DTGRP/0006/18)

The Panel considered that its comments and rulings above at Point A with regard to reduced ARV exposure applied here. In relation to the claim 'Juluca-reduce your patients' ARV exposure & potential associated toxicities', the Panel ruled breaches of the Code.

The Panel noted that in relation to reduced potential associated toxicities there were differences between the information presented on page 4 of the

leavepiece and page 3 which included the claim at issue. The Panel noted its description of page 3 at Point A above. Pages 2 and 3 presented data from the SWORD 1 and 2 studies. The Panel considered that its comments above at Point A about reduced potential associated toxicities were relevant.

The Panel noted ViiV's submission that it refuted the allegation that the claim in question was too broad or all-encompassing as it specifically highlighted that the potential associated toxicities referred to were bone and lipid changes. The Panel noted its comments above, and at Point A. In the Panel's view, it was not clear in the leavepiece that 'toxicities' referred to only bone and lipid changes given that the same section of the leavepiece featured information on other adverse events including, *inter alia*, psychiatric disorders and diarrhoea. Furthermore, the Panel disagreed with ViiV's submission that the neutral effect on serum lipids in the dolutegravir/rilpivirine group could be considered as reduction in toxicity.

Noting its comments above, including at Point A, in the Panel's view, the implication that a two-medicine regimen reduced potential associated toxicities versus a three-medicine regimen in the claim 'Juluca-reduce your patients' ARV exposure & potential associated toxicities' was ambiguous, unsubstantiated, did not reflect the available information about adverse events, and was a misleading comparison. Breaches of the Code were ruled.

ViiV exchange website

The Panel noted that it was difficult from the materials provided to ascertain the different ways a user might navigate the website and therefore the order in which information would likely be read. The Panel noted that the statement 'Juluca-reduce your patients' ARV exposure & potential associated toxicities' appeared on a page which solely discussed bone health.

In relation to the claim 'Juluca-reduce your patients' ARV exposure ...', the Panel noted its comments and rulings above at Point A which it considered applied here and ruled breaches of the Code.

In relation to the reduction in potential associated toxicities, the Panel considered that its comments at Point A above and its comments above (Point B in relation to the similar claim in the leavepiece) were relevant. The Panel noted that the only information on the webpage in question was in relation to bone health and focussed on the DEXA sub-study. In the Panel's view, the use of the plural to toxicity in the claim in question might imply that the term was used in relation to other toxicities in addition to bone. Furthermore, the Panel noted that the Juluca SPC stated in relation to this sub-study that any beneficial effect on fracture rate was not studied.

The Panel considered that the word 'associated' implied that the claimed potential reduction in toxicities was as a direct result of the claimed reduced ARV exposure. However, the data presented

on the page in relation to effects on bone compared Juluca to those continuing on a TDF based regimen. The Panel noted Gilead's submission that there was evidence that switching from a TDF-based therapy to a different triple-based therapy was also associated with significant improvements in bone markers. In the Panel's view, the page implied that a reduction in ARV exposure in general would result in a reduction in potential associated toxicities, such as the effects on bone, however, it appeared to the Panel that the nature of the medicines was an important factor. Noting its comments above, in the Panel's view, the claim 'Juluca-reduce your patients' ARV exposure and potential associated toxicities' with regard to reduced potential associated toxicities was ambiguous, unsubstantiated, did not reflect the available information about adverse events and was a misleading comparison of Juluca with triple therapy. Breaches of the Code were ruled.

C '... streamline treatment and reduce ARV exposure for your virologically suppressed HIV patients' (Journal detachable sleeve (ref VIIV/DTGRP/0002/17b(1)c))

The Panel noted that the journal detachable sleeve featured a picture of a large rucksack next to a bench and a man walking away from the bench holding a smaller rucksack. In large font was the statement 'Progress with less' and below this it stated, in smaller font, 'Look inside and discover how to streamline treatment and reduce ARV exposure for your virologically suppressed HIV patients'.

The Panel noted that the sleeve had limited information. The reference to reduction in ARV exposure was not set within any context. There was no reference to moving from a three-medicine regimen to a two-medicine regimen. The Panel noted that the claim at issue included 'streamline' and noted its comments on this point above at Point A. Notwithstanding these comments, the Panel considered that the use of 'streamline' in the statement implied that there was a comparison being made with another type of treatment, although that treatment was not identified.

The Panel noted that the sleeve was associated with the advertisement published within the journal. However, the sleeve was a separate piece of material that needed to meet the requirements of the Code. The Panel noted its comments above at Point A and considered that the claim in question regarding '... reduce ARV exposure ...' was ambiguous, unsubstantiated and a misleading comparison of Juluca with other HIV treatments. Breaches of the Code were ruled.

D 'A 2-drug regimen may reduce ARV exposure and potential associated toxicities' (Juluca Fast Facts – ViiV exchange website (ref UK/DTGRP/0005/18)).

The Panel noted the difference to the other statements considered above at points A, B and C in relation to ARV exposure; it stated 'may' reduce ARV exposure. The Panel noted its comments at points A and B above and considered that the use of the word

'may' did not make the claim any less ambiguous and ruled breaches of the Code.

In relation to the claim in question regarding reduction in potential associated toxicities, the Panel considered that it was not clear in the material what the term 'toxicities' related to. Whilst there was information on bone mineral density and lipid levels below the claim at issue, there was also information about adverse events including psychiatric disorders, nasopharyngitis, headache and diarrhoea to the left of it. In the Panel's view, in the context of this material, the term toxicities could imply any adverse event. The Panel noted its comments at Point B above in relation to lipids; in its view the neutral effect on serum lipids in the dolutegravir/rilpivirine group could not necessarily be considered a reduction in toxicity. The Panel further noted its comments at Point B above regarding the ViiV exchange website and the word 'associated'; it implied that the claimed potential reduction in toxicities was as a direct result of the claimed reduced ARV exposure. However, as previously noted above, it appeared to the Panel that the nature of the medicines in the regimen was a fundamental factor in relation to the effects on, *inter alia*, bone.

The Panel noted its comments at Point A above in relation to adverse events in the SWORD studies. In the Panel's view, the claim regarding reduction in potential associated toxicities could not be substantiated by the SWORD studies.

In the Panel's view, the implication in the claim 'a 2-drug regimen may reduce ARV exposure and potential associated toxicities' that a two-medicine regimen might reduce potential associated toxicities versus a three-medicine regimen was ambiguous, unsubstantiated, did not reflect the available information about adverse events and was a misleading comparison. Breaches of the Code were ruled.

2 Progress with less

Gilead complained about the following statements: 'For your virologically suppressed patients, PROGRESS WITH LESS (Juluca leavepiece (ref UK/DTGRP/0006/18)) and 'PROGRESS WITH LESS' (Juluca advertisement (ref VIIV/DTGRP/0002/17(1)a)).

Gilead submitted that in the claims at issue 'less' was not defined, was a hanging comparison and the claim, on its own and in the context in which it was used, implied that switching to Juluca was 'progressive', or an 'upgrade' and that a 2- medicine combination represented progress over a standard triple therapy ARV regimen. This impression was misleading, ambiguous and not capable of substantiation. Further, it created an unbalanced view that there were no risks attached to taking 'less'.

A For your virologically suppressed patients, PROGRESS WITH LESS (Juluca leavepiece (ref UK/DTGRP/0006/18))

The Panel noted that the statement appeared on the front page of the A5 bi-folded leavepiece. 'Progress with less' was in large capital letters near the top of the leavepiece and directly above it, in smaller less prominent font, was the statement, 'For your virologically suppressed HIV patients'. Below the statement was a picture of a large rucksack next to a bench and a man walking away from the bench holding a smaller rucksack. Below the picture was the statement 'A new era of HIV treatment starts today'.

The Panel noted that Juluca was indicated in adults who had been virologically suppressed on a stable regimen for at least 6 months. The Panel noted that the licensed indication was difficult to read; however, the Panel considered that the claim at issue made it clear that Juluca was not for initial therapy.

The Panel noted Gilead's submission that 'less' was a hanging comparison. The Panel noted that although the page made it clear that Juluca was a two-medicine regimen, it was not made clear what Juluca was 'less' than. Only when the leavepiece was opened would the reader see information regarding the SWORD studies and that Juluca was compared to 3-drug regimens. In the Panel's view, the reader should not have to turn a page to see the qualification to a claim. This was particularly so when considering the main claim on the front page of a leavepiece.

The statement 'A new era of HIV treatment starts today', which featured below the picture, implied that there was a comparison being made between Juluca and another HIV treatment. In the Panel's view, it was not clear exactly which HIV treatment Juluca was being compared to in the claim 'Progress with less'. Furthermore, the term 'progress' when read in conjunction with the phrase 'new era' could imply some level of improvement versus the comparator, which was not supported by the SWORD studies which showed non-inferiority of Juluca compared to continued triple therapy.

Noting its comment above, in the Panel's view the claim 'For your virologically suppressed patients, PROGRESS WITH LESS' was ambiguous, a misleading comparison of Juluca with other HIV treatment and was not capable of substantiation, as alleged, and breaches of the Code were ruled.

The Panel noted Gilead's allegation that the claim created an unbalanced view that there were no risks attached to taking 'less'. The Panel noted that it was unclear what risks Gilead was referring to. The Panel noted ViiV's submission that there was no implication that there were no side-effects or risks to using Juluca and that the leavepiece made it clear that efficacy was no better than traditional triple therapy, all of which had a well-recognized risk of failure. The Panel considered that Gilead had not proved, on the balance of probabilities, that the claim in question created an unbalanced view that there were no risks to taking 'less' and ruled no breach of the Code.

B 'PROGRESS WITH LESS' (Juluca advertisement (ref ViiV/DTGRP/0002/17(1)a))

The Panel noted that the journal advertisement had

the same picture as described above at Point 2A. 'Progress with less' was in large capital letters near the top of the advertisement. Directly above it, in smaller less prominent font, was the statement, 'For your virologically suppressed HIV patients'. Below 'Progress with less' were two bullet points which stated, 'The first single-pill, 2-drug regimen powered by dolutegravir at the core' and 'Treatment non-inferior to traditional 3-drug regimens at maintaining virological suppression at 48 weeks.'

The Panel noted that, unlike the claim at Point 2A above, the bullet points qualified that 'less' was in relation to a 2 medicine-regimen versus a 3 medicine-regimen.

Whilst the Panel noted the differences between the advertisement in question and the claim in the leavepiece at Point 2A, the Panel still considered that the word 'progress' was ambiguous and misleading. The word could imply advancement of some sort and, in the Panel's view, the claim was a misleading and an unsubstantiated comparison of Juluca compared with triple therapy. Breaches of the Code were ruled.

The Panel considered that Gilead had not proved, on the balance of probabilities, that the claim 'PROGRESS WITH LESS' created an unbalanced view that there were no risks to taking 'less' as alleged and no breach of the Code was ruled.

3 2 well-tolerated agents

Gilead complained about the following claims: 'is now available with just 2 well tolerated agents' (Juluca leavepiece (ref UK/DTGRP/0006/18)) and '2 well-tolerated agents, in 1 pill' (Juluca Fast Facts – ViiV exchange website (ref UK/DTGRP/0005/18)).

Gilead alleged that the claims were misleading as they placed undue emphasis on the safety profile of the individual components of the Juluca two medicine regimen without clarifying the safety profile of the medicine being promoted.

A 'is now available with just 2 well tolerated agents' (Juluca leavepiece (ref UK/DTGRP/0006/18))

The Panel noted that the claim at issue appeared on the back page, which appeared to be the final page of the bi-folded A5 leavepiece and was referenced to the dolutegravir and rilpivirine individual SPCs and not the Juluca SPC, however, the Juluca SPC was also included in the list of references.

The Panel noted that ViiV's submission quoted the European Public Assessment report and stated 'Based on all safety data submitted it is reasonable to conclude that the safety profile of the combined administration of DTG [dolutegravir] and RPV [rilpivirine] seems to be consistent with the established safety profiles and the current labelling of the single agents. No additional risks or safety issues were identified'.

The Panel noted ViiV's submission that the SWORD studies were conducted using the separate licensed

agents, dolutegravir and rilpivirine, as opposed to the fixed dose combination and that the Juluca European Medicines Agency (EMA) licence was underpinned by the SWORD 1 and 2 studies.

The Panel noted that page 3 of the leavepiece detailed safety results from the SWORD studies including the rates of adverse events, drug-related adverse events resulting in discontinuation (Juluca 4% vs continued 3-drug regimens <1%), and adverse events reported in ≥ 5% of subjects in the Juluca arm (psychiatric disorders 12%, nasopharyngitis 10%, headache 8% and diarrhoea 6%). Page 3 of the leavepiece also stated that in studies supporting Juluca, dolutegravir 50mg and rilpivirine 25mg were used and that bioequivalence with Juluca had been demonstrated. The Panel noted that, nonetheless, the claim should be capable of standing alone.

The Panel noted its comments above and did not consider that the claim at issue 'is now available with just 2 well tolerated agents', in the context of the leavepiece, was misleading by virtue of the emphasis on the individual components without clarifying the safety profile of Juluca, as alleged. No breach of the Code was ruled.

B '2 well-tolerated agents, in 1 pill' (Juluca Fast Facts – ViiV exchange website (ref UK/DTGRP/0005/18))

The Fast Facts sheet referred to the SWORD studies including: design, the rates of adverse events in the two treatment arms, rates of drug-related adverse events resulting in discontinuation, adverse events reported in ≥5% of subjects in the Juluca arm and that bioequivalence of Juluca to dolutegravir 50mg and rilpivirine 25mg had been demonstrated.

The Panel noted its comments above at Point 3A. The Panel did not consider that the claim '2 well-tolerated agents, in 1 pill' in the context of the material was misleading by virtue of the emphasis on the individual components without clarifying the safety profile of Juluca, as alleged. No breach of the Code was ruled.

4 Size of tablet claim

Gilead complained about the claim 'All in 1 small pill' (Juluca leavepiece (ref UK/DTGRP/0006/18)).

Gilead submitted that the claim was ambiguous as it did not clarify the actual dimensions of the Juluca tablet. Without this clarification Gilead also considered the claim was a hanging comparison, as it was unclear to the reader in comparison to what the tablet was considered small.

The Panel noted that the claim at issue featured on the back page of the bi-folded A5 leavepiece. The Panel noted that the dimensions of Juluca, as stated in the SPC, were 14 x 7mm. The Panel noted ViiV's submission that Juluca was the smallest complete single-pill HIV regimen. The Panel further noted that ViiV referred to a study by Jacobson *et al* (2016) on the sizes of commonly prescribed paediatric medicines; ViiV submitted that Juluca was

comparably on the smaller spectrum of medicines available for children. The Panel noted that Jacobson *et al* stated that common paediatric antibiotics ranged from 8 to 25mm in length, median 17mm. The Panel further noted that Juluca was indicated for use in adults only.

In the Panel's view, the description 'small' was somewhat subjective, however, the Panel did not consider that the claim was ambiguous by not stating the dimensions, as alleged. The audience was an important consideration. Noting its comments above, the Panel did not consider that the claim 'All in one small pill' was a hanging comparison or that Gilead had proved, on the balance of probabilities, that the description would be misleading to the intended audience, HIV physicians. No breach of the Code was ruled.

5 High standards

Gilead submitted that, generally, in relation to all of the above issues, ViiV had failed to maintain high standards.

The Panel noted its comments and rulings of breaches of the Code at Points 1 and 2 above. In the Panel's view, ViiV had failed to maintain high standards and a breach of the Code was ruled.

Gilead Sciences Europe Limited complained about the promotion of Juluca (dolutegravir/rilpivirine) by ViiV Healthcare. Juluca was a combination of two antiretroviral (ARV) medicines used in the treatment of human immune deficiency virus type-1 (HIV-1) infection in adults who were virologically-suppressed on a stable ARV regimen for at least 6 months. Gilead also marketed ARV combination medicines for the treatment of HIV.

Gilead stated that inter-company dialogue with ViiV had been unsuccessful on a number of matters which it was now raising as a complaint.

1 Reduction of antiretroviral (ARV) exposure and potential associated toxicities

Gilead complained about the following statements: 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure & potential associated toxicities' (Juluca leavepiece (ref UK/DTGRP/0006/18)); 'Juluca – reduce your patients' ARV exposure & potential associated toxicities' (ViiV exchange website (ref UK/DTGRP/0034/18(1))); '... streamline treatment and reduce ARV exposure for your virologically suppressed HIV patients' (Journal detachable sleeve (ref ViiV/DTGRP/0002/17b(1)c)); 'A 2- drug regimen may reduce ARV exposure and potential associated toxicities' (Juluca Fast Facts – ViiV exchange website (ref UK/DTGRP/0005/18)).

COMPLAINT

Gilead stated that whilst each statement was slightly different, the following two claims were made in the context of the promotion of Juluca, a combination of two medicines for the treatment of HIV in virally suppressed patients:

- (iii) reducing the number of ARV medicines from [not stated] to two would reduce a patient's ARV exposure;
- (iv) this reduction translated into a reduction in potential associated toxicities.

Gilead considered these statements and claims were inaccurate, ambiguous, misleading, could not be substantiated and did not reflect the available evidence on adverse events, in breach of Clauses 7.2, 7.3, 7.4 and 7.9 of the Code.

Gilead submitted that the claim that moving to a two-medicine regimen would reduce a patient's ARV exposure was stated without any qualification and as such asserted that this would always be the case, regardless of which medicines the patient switched from and which medicines the patient switched to. Whilst a switch to a two-medicine regimen reduced the number of ARV medicines being taken by the patient, Gilead did not accept that this would necessarily reduce the patient's ARV exposure and such a claim must be substantiated.

The extent of ARV exposure was not measured by the number of individual medicines being taken but by the amount of ARV the patient was exposed to by the regimen he/she took. Factors such as the amount of active ingredient in each ARV medicine were also relevant to the level of ARV exposure.

Further, when considering ARV exposure, both the pharmacokinetic and pharmacodynamic properties of the medicines must be considered (ie both medicine plasma/tissue levels and the pharmacodynamic properties of the individual components). This was particularly relevant in the context of any comparison between three medicine regimens and two medicine regimens when the components of each of the regimens did not match (and even if they did, there should be no interaction that affected the pharmacokinetic properties of each of the remaining components when switching from 3 to 2 medicines). In other words, ARV exposure could only be discussed as a potential variable if there was a comparison between a 3 medicine and 2 medicine combination comprising of the same components, and where the pharmacokinetics of each of the remaining components were unaffected by the removal of a third medicine.

The main clinical study data for Juluca was the SWORD study (Llibre *et al* 2018). No data on the pharmacokinetic assessment on the individual components had been presented in the context of that study or supplied in response to this complaint. Instead, the SWORD study involved a switch from a triple combination HIV regimen (ie three medicines) to a regimen of dolutegravir and rilpivirine; 87% of patients who switched to dolutegravir and rilpivirine had not previously been exposed to those two medicines and so switched to two medicines that had different pharmacokinetic and pharmacodynamic properties compared with their original triple regimens.

Gilead stated that the claim that switching to a two-medicine regimen would reduce potential associated toxicities was also stated without any qualification

and claimed, both generally and specifically in relation to Juluca, that a switch to a two medicine ARV regimen would result in a reduction of potential toxicities.

For the reasons identified above, Gilead did not accept that a switch from triple therapy to two ARV medicines would necessarily reduce a patient's ARV exposure. Further, as the two medicines combined in Juluca (dolutegravir and rilpivirine) might have different pharmacokinetic and pharmacodynamic properties to the original three ARV medicines the patient was switched from, Gilead considered it was misleading to assert that any differences in tolerability or safety that might arise from the switch to two medicines were a general function of reduced ARV exposure. This was an inaccurate, misleading and ambiguous claim.

In any event, the claim that a switch to Juluca would reduce potential associated toxicities must be substantiated. The SWORD study demonstrated that numerically more participants who switched to dolutegravir and rilpivirine reported adverse events leading to withdrawal when compared with patients remaining on triple regimens (17 (3%) vs 3 (<1%)). As a further example, in the SWORD study, neuropsychiatric adverse events were observed to be significantly increased in patients who switched to Juluca - 61 (12%) psychiatric disorders vs 32 (6%) in the control arm; further, 7 discontinuations for psychiatric disorders and 1 discontinuation for nervous system disorders occurred in the Juluca arm vs 1 discontinuation due to psychiatric disorders in the control arm at 48 weeks.

The prominent focus on the 'potential' benefit of 'reducing ARV exposure' on toxicity without balancing appropriately with the potential risks was misleading and unbalanced, and the use of the broad term 'toxicity' without clarification as to what level of adverse event was considered to fall within the term, made the claim ambiguous.

Clarification and qualification was required as there was no universally accepted definition of 'toxicity'. It was clear from studies relating to dolutegravir that the term was not reserved for events that resulted in permanent damage or long-term harm – eg the seminal Dutch study, 'Unexpectedly High Rate of Intolerance for Dolutegravir in Real Life Setting', (Van den Berk *et al* 2016), a poster presented at AIDS 2016 (de Boer *et al* 2016), and an associated peer reviewed publication on a German cohort study (Hoffmann *et al* 2017, 'Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients') which described the real world clinical experience of dolutegravir – one of the components of Juluca – the authors characterised the gastrointestinal and/or neuropsychiatric side-effects observed with dolutegravir as 'toxicities' even though they emerged over a median of 78 days, or within 12 months, respectively.

Further, all claims made the generalisation that there was a potential for reduced toxicity when switching from any combination of three medicines to Juluca, without clarification that the ARV medicines being switched from and to was relevant, and the claims

failed to adequately disclose that the majority (70%) of patients on triple therapy in the SWORD study were on a tenofovir disoproxil fumarate (TDF)-based regimen. A large body of evidence supported that switching from TDF-based therapy (a therapy associated with renal events and bone loss) to emtricitabine/tenofovir alafenamide (F/TAF) based triple therapy was also associated with significant improvements in renal and bone markers, which further highlighted that the nature of medicines used was important in reducing potential toxicities, not just the number of medicines.

Whilst information about adverse events, bone mineral density and DEXA measures was included in the UK leavepiece (ref UK/DTGRP/0006/18) immediately after the phrase 'reduce your patients' ARV exposure and potential associated toxicities', this was not always the case, eg the Juluca fast facts infographic from the ViiV Exchange website (UK/DTGRP/0005/18) and even with the UK leavepiece, Gilead asserted that this did not provide adequate clarification and qualification for the broad claim of 'reduce potential associated toxicities' due to:

- the prominence of that claim on pages 3 and 4 of the piece
- unqualified use of 'toxicities' as distinct from 'safety' as outlined above
- the all-encompassing title which implied that a number of safety (toxicity) issues could be avoided, even though the only substantiating evidence was an improvement in bone mineral density and renal at week 48, restricted to those patients who were switched from a TDF-based triple ARV regimen. Gilead did not accept that maintenance of lipid levels could reasonably be claimed as avoiding future safety issues vs comparator
- an imbalance in the prominence of the rates of neuropsychiatric toxicity observed with Juluca on page 3
- the characterisation of the rates of neuropsychiatric toxicity observed with Juluca on page 3 ('few' medicine-related adverse events resulted in discontinuation).

The clear communication objective of all of the campaign pieces was to assert that by switching from ARV triple therapy to Juluca, there was always a reduction in ARV exposure which translated to a potential (or actual) reduction [sic?] in tolerability or safety. Any statements of this nature that made any relevant claims around potential improvements in long-term safety must be limited to those which were accurate, balanced, objective, unambiguous and capable of substantiation and Gilead did not consider this test had been met in the Juluca promotional material in question. Gilead alleged breaches of Clauses 7.2, 7.3, 7.4 and 7.9.

RESPONSE

ViiV submitted that Gilead seemed to have conflated a number of claims and pieces of material into one overarching complaint whilst acknowledging each statement was slightly different. Gilead had alleged breaches of the Code in relation to the claim that reducing the number of ARV medicines from three

to two would reduce a patient's ARV exposure. ViiV stated that it strongly refuted this allegation for general and specific reasons.

ViiV refuted the allegations in general as it considered that the statement that changing from three ARVs to two ARVs would represent a reduction in exposure to ARVs was self-evident.

ViiV also considered that the concept was clearly understood by HIV physicians. In the scientific literature, commonly studied and cited approaches to reducing ARV exposure without compromising the efficacy of treatment included reducing the number of medicines within a regimen.

ViiV explained that over the past twenty years HIV physicians had prescribed a combination of three or even four ARVs to be taken together to suppress the HIV virus. Different ARVs had been used simultaneously to minimise the chance that the virus developed resistance to treatment. But, as the treatment of HIV was currently life-long, and all treatments carried risks as well as benefits, there was concern that this polypharmacy approach might lead to significant long-term toxicities for patients. Hence there was interest in various simplification strategies to reduce the patient's exposure to ARVs including reducing the number of medicines used.

ViiV noted that Gilead had tried to complicate this reality with a discussion of the ingredients, pharmacokinetic and pharmacodynamic properties of individual medicines. Yet regardless of the individual properties of an ARV – all currently available ARVs required daily dosing which suggested broadly similar exposure to them from a patient and clinical perspective – a reduction from three to two medicines still represented reduced exposure to whatever those cumulative properties might be.

ViiV noted that Gilead failed to provide any specific evidence where reducing the ARV number from three to two resulted in any outcome other than a decrease in ARV exposure.

More specifically ViiV disputed the allegations in relation to the use of the term 'reduced ARV exposure' in the promotion of Juluca. Firstly, Juluca was a two-medicine regimen of dolutegravir and rilpivirine. Secondly, the available data supported its use as an effective treatment in certain HIV-positive patients. The Juluca FDA/EMA licence was underpinned by the SWORD 1 and 2 studies; these two, fully powered, randomised controlled trials recruited patients with a suppressed viral load who had taken conventional HIV treatment containing at least three medicines and successfully switched them to the two-medicine regimen of dolutegravir and rilpivirine, thereby reducing exposure through reducing the number of medicines within their treatment regimen while maintaining viral suppression. There were also several peer reviewed publications which described the rationale for reducing exposure and referenced dolutegravir plus rilpivirine and the SWORD studies.

ViiV noted that on the Juluca leavepiece, the ViiV exchange website and on the ViiV exchange Juluca

Fast-Facts, the claims of reducing ARV exposure were made clearly within the context of switching therapy from the standard three ARVs to Juluca, a two-medicine regimen. The study design was included and multiple references were made with respect to switching from three to two medicines.

In the advertisement (ref VIIV/DTGRP/0002/17(I) a), the claims of reducing ARV exposure were made clearly within the context of switching therapy from the standard three ARVs to Juluca, a two-medicine regimen with two prominent bullet points immediately beneath the headline indicating that Juluca was the first single pill, two medicine regimen and it had shown non-inferiority to traditional three medicine regimens. The materials were aimed at expert HIV physicians who well understand that current standard regimens contain three or four ARVs and therefore Juluca being a complete regimen consisting of only two ARVs was clearly less ARV exposure.

ViiV noted that Gilead had further alleged breaches of the Code in relation to the claim that a reduction in ARVs translated into a reduction in potential associated toxicities.

ViiV strongly refuted the allegation for general and specific reasons. ViiV's general reasoning was that logic dictated that reducing the number of ARVs from three or four to two resulted in decreased exposure to ARVs and the toxicities related to them.

ViiV stated that those involved in HIV care would reach the same conclusion. For example, ViiV noted that a UK HIV physician, currently President of the International AIDS Society, referred to the use of two rather than three ARVs in the August 2018 *British Medical Journal* article by simply stating 'You reduce toxicity' (Pozniak, 2018).

Similarly, in the *Lancet*, Llibre *et al* (2018) made it clear that use of Juluca would avoid the major NRTI (nucleoside reverse transcriptase inhibitors) toxicities; 'Once-daily oral dolutegravir-rilpivirine would be the first oral two-drug regimen that provides patients with an alternative to guideline-preferred triple-drug regimens, avoids major NRTI toxicities, has limited potential for drug-drug interactions, and does not increase lipid concentrations or inflammatory biomarkers'.

ViiV noted that Gilead had referred to adverse events and toxicity interchangeably in its complaint. ViiV disagreed with this approach as it observed that adverse events and toxicity were often considered separately in both the reporting of HIV studies and in practice by HIV physicians. In fact, Gilead also made this distinction when it reported adverse events and toxicity in a number of publications.

More specifically Gilead suggested that the adverse event reports from the SWORD 1 and 2 studies did not support claims related to reduced toxicity of dolutegravir and rilpivirine. Gilead noted that numerically more participants switching to dolutegravir and rilpivirine reported adverse events

leading to withdrawal when compared with patients remaining on triple therapy.

In response, and in addition to highlighting again the bundling of the terms adverse events and toxicity, ViiV stated that an explanation for these adverse event findings resided more in the study design than the characteristics of the medicines themselves. The Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency recognised in the European Public Assessment Report (EPAR) for Juluca the particular difficulties of reporting adverse events in an open-label switch trial, where the comparator arm remained on therapy that the patients had been stable on for at least six months, stating 'Firstly, it can be assumed that many AEs occur at the beginning of therapy so that subjects on stable therapy (i.e. subjects in the CAR ["Current antiretroviral"] treatment group) would report less AEs than those randomised to a new therapy regimen (i.e. subjects in the dolutegravir and rilpivirine treatment group). Comparing subjects stable on CAR with subjects newly switched to dolutegravir and rilpivirine can therefore be expected to create a bias in favour of CAR. An analysis of the timing of occurrence of adverse events relative to the start of dolutegravir and rilpivirine / CAR treatment showed a shorter median time to onset in the dolutegravir and rilpivirine group compared to the CAR group. This observation reinforces the assumption that the higher incidence of AEs in the dolutegravir and rilpivirine treatment group vs CAR group is mainly due to the fact that subjects in the dolutegravir and rilpivirine group were not familiar with the adverse events of this treatment while the subjects on the CAR arm were already on their regimen for at least 6 months and thereby somewhat selected for tolerating the treatment'.

In terms of toxicities themselves the safety analyses of the SWORD 1 and 2 studies showed an improvement in a marker of toxicity as Gilead acknowledged in its complaint ('... the only substantiating evidence is an improvement in BMD and renal at week 48 ...'). The studies focused on some of the established long-term toxicities associated with ARVs, ie bone destruction (primarily a toxicity of NRTIs) and altered lipids (primarily a toxicity of protease inhibitors). As stated in the Juluca summary of product characteristics (SPC), the mean bone mineral density (BMD) increased in a DEXA sub-study from baseline to week 48 in subjects who switched to dolutegravir and rilpivirine (1.34% total hip and 1.46% lumbar spine) compared with those who continued on treatment with a tenofovir disoproxil fumarate (TDF) containing antiretroviral regimen, and thus indicated a reduction in the well-established deleterious effect on BMD that NRTIs might have. With respect to the maintenance of lipid levels, this was relevant as TDF was well recognised to be beneficial in lowering lipid levels and ViiV considered that it was important to demonstrate that this benefit was maintained when switching to dolutegravir and rilpivirine. The authors stated: '... we noted a neutral effect on serum lipids in the dolutegravir- rilpivirine group, despite more than 70% of these participants being switched from tenofovir disoproxil fumarate, which has been

reported to be a lipid-friendly drug'. ViiV noted that Gilead also commented that in the study population within SWORD 1 and 2, 70% of patients took a triple regimen which included TDF and that another combination of ARVs was also associated with significant improvements in renal and bone markers when compared to TDF-containing regimens. Gilead was referring to the use of tenofovir alafenamide (TAF), another pro-drug of tenofovir which was still an NRTI, a type of ARV which was well recognized as having the potential for deleterious long-term effects such as bone or renal toxicity. Juluca was the only licensed regimen that was NRTI-sparing and therefore although TAF might have less impact on these areas than TDF, it was still an NRTI and carried some risk of NRTI toxicities.

ViiV noted that the SWORD studies included multiple ARV combinations; the predominance of TDF was consistent with practice within the UK given it was the most commonly used NRTI in the UK and was a preferred agent in combination with other ARVs in both the British HIV Association and multiple international guidelines. This significant reversal in bone toxicity when switching away from a TDF containing regimen was a proxy for how avoidance of an additional medicine in any regimen could prevent known or unknown toxicities that might be attributed to that medicine.

ViiV noted Gilead's various allegations regarding the manner of presentation of the claims 'reduce potential associated toxicities' in the leavepiece [UK/DTGRP/0006/18]. ViiV disagreed that the claim was too broad or all-encompassing as the company specifically highlighted that potential associated toxicities referred to bone and lipid changes.

Gilead also asserted there was an 'imbalance in the prominence of the rates of neuropsychiatric disorders in the leavepiece', but the commonest adverse events (those occurring in >5%) in the Juluca arm were clearly listed with similar prominence to other adverse events, along with the frequency of their occurrence. The first of these was psychiatric (12%), reflecting Table 2 of the publication of the SWORD 1 and 2 studies.

Gilead also had concerns over 'the characterisation of the rates of neuropsychiatric toxicity observed with Juluca on page 3 ("few" drug-related AEs resulted in discontinuation)'. The characterisation of the rates was specific and clear – the bullet point clearly stated 'psychiatric disorders (12%)'. Of these, the authors stated 'Most neuropsychiatric adverse events were grade 1 or 2 and not considered to be related to dolutegravir/rilpivirine'.

ViiV submitted that the discontinuations due to medicine-related adverse events was clearly stated as being 3%, so readers were in no doubt what was meant by 'few'. Of these only 1% were due to psychiatric disorders.

In summary, ViiV believed that a change from three to two of the currently available ARVs could appropriately be described as reducing exposure to them and their associated potential toxicities, that

it was appropriate to make such claims with Juluca, that the information was presented in fair and balanced manner and that ultimately there was no breach of Clauses 7.2, 7.3, 7.4 and 7.9.

PANEL RULING

The Panel noted Gilead's allegation that four similar statements were in breach of the Code. The Panel noted that there were two overarching allegations: the claim that reducing the number of ARV medicines in a regimen from three to two would reduce a patient's ARV exposure, and the claim that this reduction translated into a reduced potential for associated toxicities.

The Panel considered each statement separately in the context of the material in which it appeared.

The two allegations were ruled upon separately in each of the statements at issue.

A 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure & potential associated toxicities' (Juluca leavepiece (ref UK/DTGRP/0006/18))

The Panel noted that the statement at issue included 'streamline' and further noted that ViiV had agreed following inter-company dialogue to withdraw materials that used this term. The Panel therefore made no ruling with regard to the reference to 'streamline'.

The Panel noted that the claim at issue appeared as a heading on the back page of the 4 page bi-folded A5 leavepiece which appeared to the Panel to be the final page that a user would read. Above the claim at issue, in smaller less prominent font, was the statement, 'Based on the SWORD study results ...' and below the claim at issue were three further statements, in numerical descending bullet points: 'Juluca is non-inferior to 3-drug regimens at maintaining virological suppression ...', 'is now available with just 2-well-tolerated agents ...', 'all in 1 small pill'.

The Panel noted that SWORD-1 and SWORD-2 were Phase III, open-label, randomised, 48-week studies which demonstrated that dolutegravir 50mg plus rilpivirine 25mg (a two-drug regimen) was non-inferior to the continuation of triple ARV therapy (two nucleoside reverse transcriptase inhibitors plus either an integrase strand transfer inhibitor, non-nucleoside reverse transcriptase inhibitor or protease inhibitor) in maintaining virological suppression over 48 weeks, in adults who had been stable for at least 6 months (Llibre *et al*, 2018). The Panel noted ViiV's submission that the Juluca European Medicines Agency licence was underpinned by the SWORD-1 and SWORD-2 studies and that Juluca had demonstrated bioequivalence to dolutegravir 50mg plus rilpivirine 25mg.

The Panel noted Gilead's assertion that switching from a three-medicine regimen to a two-medicine regimen reduced the number of ARV medicines taken by a patient but did not necessarily reduce the patient's ARV exposure and such a claim required

substantiation. The Panel further noted Gilead's submission that the extent of ARV exposure was not measured by the number of individual medicines but by the amount of ARV the patient was exposed to by the regimen and factors such as amount of active ingredient in each ARV, and the pharmacokinetic and pharmacodynamic properties of the medicines was relevant to the level of ARV exposure. The Panel noted Gilead's assertion that ARV exposure could only be discussed as a potential variable if there was a comparison between a 3-medicine and a 2-medicine combination comprising of the same components, and where the pharmacokinetics of each of the remaining components was unaffected by the removal of the third medicine. Gilead had argued that no data on the pharmacokinetics of the individual components had been presented in the context of the SWORD studies or supplied by ViiV in response to the complaint. Furthermore, 87% of patients who switched to dolutegravir/rilpivirine from triple therapy had not previously been exposed to these two medicines, which had different pharmacokinetic and pharmacodynamic properties compared to the original 3 medicines the patient had taken.

The Panel noted ViiV's response that it was a self-evident statement of fact that changing from three to two ARVs represented a reduction in exposure to ARVs; all those currently available required daily dosing suggesting broadly similar exposure and a reduction from three to two medicines still represented reduced exposure to whatever those cumulative properties might be. ViiV noted that Gilead had not provided any specific evidence where a reduction from three to two ARVs resulted in any outcome other than a decrease in ARV exposure.

The Panel noted that neither ViiV nor Gilead had referred to any specific pharmacokinetic data. The Panel considered that ViiV had taken a very general view of the claim in question and had not addressed Gilead's point about the pharmacokinetics and pharmacodynamics of individual medicines in a regimen and overall ARV exposure.

The Panel noted that the published literature supplied by ViiV discussed different ways ARV exposure could be reduced, which included, *inter alia*, reference to fewer drugs (Katlama *et al* 2017) and the Panel noted ViiV's submission that this was a concept clearly understood by HIV physicians. It appeared to the Panel that the published literature provided by ViiV used terminology that suggested fewer medicines in an ARV regimen translated into reduced ARV exposure, without considering the specific properties of each medicine in the regimen. The Panel noted that, nonetheless, matters that appeared in published peer-reviewed journals might be found in breach of the Code when featured in company material.

The Panel understood that drug exposure was a defined term in clinical pharmacology and it could be affected by numerous factors. The Panel noted that the statement at issue was in relation to ARV exposure and therefore encompassed all medicines within an ARV regimen. In the Panel's

view, a reduction from a 3-medicine to a 2-medicine regimen reduced the number of ARV medicines that a patient was exposed to but it might not necessarily reduce the patient's ARV exposure as a measure of the concentration of ARV medicine in the body with respect to time; there were many factors to be considered, *inter alia*, dosage and interactions which could affect the clearance of one or more of the medicines in the regimen. Context and the audience were also important. The Panel noted that the statement at issue was below the caveat 'Based on the SWORD study results ...'. The Panel further noted ViiV's submission that the SWORD studies included multiple ARV combinations in the comparator arm. The Panel noted, however, that the Llibre *et al* publication did not discuss exposure in subjects switching from triple therapy to dolutegravir/rilpivirine in terms of quantitative measures of total systemic drug exposure such as area under the curve (AUC). The Panel considered that the claim in question 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure and potential associated toxicities' was such that some HIV physicians might consider that there was pharmacokinetic drug exposure data for dolutegravir/rilpivirine versus the different triple therapy combinations in, *inter alia*, the SWORD studies and that was not so.

The Panel noted its comments above. In the Panel's view, and on balance, treatment with a two-medicine regimen did not necessarily mean that there was a reduction in ARV exposure versus treatment with a three-medicine regimen. The properties of each medicine in the regimen were relevant to ARV exposure. In this regard, the Panel considered that the reference to a two-drug regimen reducing ARV exposure versus a three-drug regimen in the claim 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure & potential associated toxicities' was ambiguous, unsubstantiated and a misleading comparison. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

The Panel noted Gilead's allegation regarding the claim in the second half of the statement at issue which suggested that a reduction in ARV exposure reduced potential associated toxicities.

The Panel noted Gilead's submission that there was no universally accepted definition of toxicity. The Panel noted Gilead's argument that the broad term 'toxicity' without any clarification as to what level of adverse event was considered to fall within the term made the claim ambiguous. Furthermore, the Panel noted Gilead's allegation that all claims made the generalisation that there was a potential for reduced toxicity when switching from any combination of three medicines to Juluca; and ViiV had failed to adequately disclose that the majority (70%) of patients on triple therapy in the SWORD studies were taking a tenofovir disoproxil fumarate (TDF) based regimen, which was associated with renal events and bone loss.

The Panel noted Gilead's argument that there was a large body of evidence that switching from a TDF-based therapy to a different triple-based therapy

(emtricitabine/tenofovir alafenamide) was also associated with significant improvements in renal and bone markers which highlighted that the nature of drugs, not just the number of drugs, was relevant in relation to reducing potential toxicities. The Panel noted ViiV's submission that Juluca was the only licensed regimen that was NRTI-sparing and that the significant reversal in bone toxicity when switching away from a TDF containing regimen was a proxy for how avoidance of an additional medicine in any regimen could prevent known or unknown toxicities that might be attributed to that medicine.

The Panel noted that the Llibre *et al* publication referred to adverse events, including a breakdown from grade 1 to 4. The Panel considered that the use of the term 'toxicity' was ambiguous in relation to the SWORD study results and it was unclear if it related to a particular grade or type of adverse event.

The Panel noted ViiV's submission that logic dictated that reducing the number of ARVs from four/three to two resulted in decreased exposure to ARVs and the toxicities related to them. In the Panel's view, the profile of the medicines moved from and to needed to be acknowledged and the use of the word 'potential' in reference to toxicities did not remove the need for substantiation. The Panel noted ViiV's submission that the SWORD studies showed improvements in long-term toxicities associated with ARVs, namely bone destruction, which was primarily a toxicity of NRTIs, and altered lipids, which was primarily a toxicity of protease inhibitors.

The Panel noted that the bottom half of page 3, the preceding page of the leavepiece, had the heading 'Juluca – reduce your patients' ARV exposure & potential associated toxicities' beneath which were claims regarding statistically significant recovery in bone mineral density and maintained lipid levels at 48 weeks. Within the same section of the leavepiece were statements related to adverse events, including rates of all adverse events, drug-related adverse events resulting in discontinuation and adverse events reported in >5% of subjects in the Juluca arm including psychiatric disorders, nasopharyngitis, headache and diarrhoea. The heading 'Juluca – reduce your patients' ARV exposure & potential associated toxicities', was separately subject to complaint at section B below; however, the Panel considered that this section of the leavepiece was relevant to the claim at issue on the back page (page 4). The Panel considered that the information on page 3 implied that the term 'toxicities' related to all types of adverse events and this implication was relevant to consideration of the claim in question on page 4.

The Panel noted that after switching to dolutegravir/rilpivirine, more subjects (77%) reported at least one adverse event by week 48 compared with subjects who continued with current ARVs (71%). Furthermore, adverse events stratified by grades 1 to 4 were either the same between the two treatment arms or higher with dolutegravir/rilpivirine. The Panel noted ViiV's submission that it could be assumed that many adverse events occur at the beginning of therapy so that subjects continuing

on current ARV therapy would report less adverse events than those randomised to a new therapy (ie the dolutegravir/rilpivirine group). The Panel noted that the statement at issue was below the caveat 'Based on the SWORD study results ...' and, in the Panel's view, the claim 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure and potential associated toxicities' with regard to reduction in potential associated toxicities could not be substantiated by the SWORD study results.

The Panel noted its comments above. In the Panel's view, the implication that a two-medicine regimen reduced potential associated toxicities versus a three-medicine regimen in the claim 'Streamline treatment with a 2-drug regimen & reduce your patients' ARV exposure & potential associated toxicities' was ambiguous, unsubstantiated, did not reflect the available information about adverse events and was a misleading comparison. Breaches of Clauses 7.2, 7.3, 7.4 and 7.9 were ruled.

B 'Juluca-reduce your patients' ARV exposure and potential associated toxicities' (Juluca leavepiece (ref UK/DTGRP/0006/18) and ViiV exchange website (ref UK/DTGRP/0034/18(1)))

Juluca leavepiece (ref UK/DTGRP/0006/18)

The Panel considered that its comments and rulings above at Point A with regard to reduced ARV exposure applied here. In relation to the claim 'Juluca-reduce your patients' ARV exposure & potential associated toxicities', the Panel ruled a breach of Clauses 7.2, 7.3 and 7.4.

The Panel noted that in relation to reduced potential associated toxicities, there were differences between the information presented on page 4 of the leavepiece and page 3 which included the claim at issue. The Panel noted its description of page 3 at Point A above. Pages 2 and 3 presented data from the SWORD 1 and 2 studies. The Panel considered that its comments above at Point A about reduced potential associated toxicities were relevant.

The Panel noted Gilead's allegation that there was inadequate clarification or qualification of the broad claim of 'reduce potential associated toxicities' due to, *inter alia*, the prominence of the claim on pages 3 and 4 of the leavepiece, the unqualified use of 'toxicities' as distinct from 'safety', the all-encompassing title which implied that a number of safety (toxicity) issues could be avoided, an imbalance in the prominence of the rates of neuropsychiatric toxicity observed with Juluca and the characterisation of these rates in the statement 'few drug-related AEs resulted in discontinuation'.

With regard to the comments regarding psychiatric adverse events, the Panel noted ViiV's submission that the rate was stated in the leavepiece as 'psychiatric disorders (12%)'. The Panel noted ViiV's submission that the discontinuations due to medicine-related adverse events was clearly stated as being 3%, so readers were in no doubt what was meant by 'few', and that only 1% of these

were due to psychiatric disorders. The Panel noted that the leavepiece stated that 4% of the Juluca group discontinued due to drug-related adverse events; there was no mention of how many subjects withdrew due to drug-related psychiatric adverse events. The Panel considered that the use of the word 'few' in relation to 4% was not unreasonable.

The Panel noted ViiV's submission that it refuted the allegation that the claim in question was too broad or all-encompassing as it specifically highlighted that the potential associated toxicities referred to were bone and lipid changes. The Panel noted its comments above, and at Point A. In the Panel's view, it was not clear in the leavepiece that 'toxicities' referred to only bone and lipid changes given that the same section of the leavepiece featured information on other adverse events including, *inter alia*, psychiatric disorders and diarrhoea.

Furthermore, the Panel disagreed with ViiV's submission that the neutral effect on serum lipids in the dolutegravir/rilpivirine group could be considered as reduction in toxicity.

Noting its comments above including at Point A, in the Panel's view, the implication that a two-medicine regimen reduced potential associated toxicities versus a three-medicine regimen in the claim 'Juluca- reduce your patients' ARV exposure & potential associated toxicities' was ambiguous, unsubstantiated, did not reflect the available information about adverse events, and was a misleading comparison. Breaches of Clauses 7.2, 7.3, 7.4 and 7.9 were ruled.

ViiV exchange website

The Panel noted that it was difficult from the materials provided to ascertain the different ways a user might navigate the website and therefore the order in which information would likely be read. The Panel noted that the statement 'Juluca-reduce your patients' ARV exposure & potential associated toxicities' appeared on a page which solely discussed bone health. From the screen shots provided, the previous page appeared to feature information regarding rates of virological failure vs continued triple therapy and the subsequent page featured information regarding lipid values and rates of adverse events from the SWORD studies. The Panel noted that there was a similar statement on another page titled 'Welcome to the 2-Drug Regimen Era', which stated 'Streamlining therapy to 2 drugs following suppression can reduce ARV exposure and potential associated toxicities'; however, that specific statement was not identified by Gilead and therefore not considered by the Panel.

The Panel noted that the claim at issue 'Juluca-reduce your patients' ARV exposure & potential associated toxicities' appeared as a heading on the webpage in question directly above the statement, in smaller font, 'Juluca-statistically significant Recovery in Bone Mineral Density (Dexa Sub-Study)'. Beneath were two side-by-side graphs which showed the change in hip and lumbar bone mineral density (BMD) for Juluca versus continued triple therapy.

Below the graphs were two bullet points with statements regarding the % improvement in hip and lumbar spine bone mineral density and the decrease in measured markers of bone turnover for Juluca compared with patients continuing a TDF-based regimen. A highlighted box at the bottom of the webpage featured the heading 'Switching to Juluca provides a robust option for maintaining virological suppression while preserving bone health' above what appeared to be two videos: bone health and HIV and the effect of dolutegravir/rilpivirine on BMD in the SWORD studies.

In relation to the claim 'Juluca-reduce your patients' ARV exposure ...' the Panel noted its comments and rulings above at Point A which it considered applied here and ruled a breach of Clauses 7.2, 7.3 and 7.4.

In relation to the reduction in potential associated toxicities the Panel considered that its comments at Point A above and its comments above (Point B in relation to the similar claim in the leavepiece) were relevant. The Panel noted that the only information on the webpage in question was in relation to bone health and focussed on the DEXA sub-study. In the Panel's view, the use of the plural to toxicity in the claim in question might imply that the term was used in relation to other toxicities in addition to bone. Furthermore, the Panel noted that the Juluca SPC stated in relation to this sub-study that any beneficial effect on fracture rate was not studied.

The Panel considered that the word 'associated' implied that the claimed potential reduction in toxicities was as a direct result of the claimed reduced ARV exposure. However, the data presented on the page in relation to effects on bone compared Juluca to those continuing on a TDF based regimen. The Panel noted Gilead's submission that there was evidence that switching from a TDF-based therapy to a different triple-based therapy was also associated with significant improvements in bone markers. In the Panel's view, the page implied that a reduction in ARV exposure in general would result in a reduction in potential associated toxicities, such as the effects on bone, however, it appeared to the Panel that the nature of the medicines was an important factor. Noting its comments above, in the Panel's view, the claim 'Juluca-reduce your patients' ARV exposure and potential associated toxicities' with regard to reduced potential associated toxicities was ambiguous, unsubstantiated, did not reflect the available information about adverse events and was a misleading comparison of Juluca with triple therapy. Breaches of Clauses 7.2, 7.3, 7.4 and 7.9 were ruled.

C '...streamline treatment and reduce ARV exposure for your virologically suppressed HIV patients' (Journal detachable sleeve (ref VIIIV/DTGRP/0002/17b(1c))

The Panel noted that the journal detachable sleeve featured a picture of a large rucksack next to a bench and a man walking away from the bench holding a smaller rucksack. In large font was the statement 'Progress with less' and below this it stated, in smaller font, 'Look inside and discover how to streamline treatment and reduce ARV exposure for

your virologically suppressed HIV patients'. The Panel noted that this piece of material was withdrawn by ViiV during inter-company dialogue in relation to the claim 'Progress with less'. As the material was not withdrawn due to the claim in question regarding reduced ARV exposure, the case preparation manager decided that the complaint regarding the claim at issue in this material should proceed.

The Panel noted that the sleeve had limited information. The reference to reduction in ARV exposure was not set within any context. There was no reference to moving from a three-medicine regimen to a two-medicine regimen. The Panel noted that the claim at issue included 'streamline' and noted its comments on this point above at Point A. Notwithstanding these comments the Panel considered that the use of 'streamline' in the statement implied that there was a comparison being made with another type of treatment, although that treatment was not identified.

The Panel noted that the sleeve was associated with the advertisement published within the journal. However, the sleeve was a separate piece of material that needed to meet the requirements of the Code. The Panel noted its comments above at Point A and considered that the claim in question regarding '... reduce ARV exposure ...' was ambiguous, unsubstantiated and a misleading comparison of Juluca with other HIV treatments. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled accordingly.

D 'A 2- drug regimen may reduce ARV exposure and potential associated toxicities' (Juluca Fast Facts – ViiV exchange website (ref UK/DTGRP/0005/18))

The Panel noted that the Juluca Fast Facts material was A4 in size and double-sided. One side included statements about Juluca and the reverse side included the brand logo, prescribing information and a list of references.

The material featured Juluca's indication and the claim 'The first 2-drug regimen in a single pill'. A picture of the pill with its dimensions and components was displayed along with the statement 'powered by dolutegravir at the core'. Below this was information regarding the design of the SWORD studies and a statement that bioequivalence between Juluca and dolutegravir 50mg plus rilpivirine 25mg had been demonstrated. The statement 'JULUCA – non-inferior to continued 3-drug regimens in maintaining virological suppression at 48 weeks' appeared in the middle of the page above results from the studies, including rates of adverse events, drug-related adverse events resulting in discontinuation and adverse events reported in ≥5% of subjects in the Juluca arm. To the right of this, and separated by a vertical line, was the claim in question 'A 2-drug regimen may reduce ARV exposure and potential associated toxicities', which was the statement at issue in the complaint. Directly below the claim was the number three with an arrow pointing to the number 2, followed by the statements '2 well-tolerated agents, in 1 pill', 'Statistically significant recovery in bone mineral density (DEXA

sub-study)', 'Maintains lipid levels'. Further below and at the bottom of the page was information regarding key drug interactions and how to prescribe Juluca.

Turning to the claim at issue, 'a 2- drug regimen may reduce ARV exposure and potential associated toxicities', the Panel noted the difference to the other statements considered above at points A, B and C in relation to ARV exposure; it stated 'may' reduce ARV exposure. The Panel noted its comments at points A and B above and considered that the use of the word 'may' did not make the claim any less ambiguous. The Panel noted its comments above at Points A and B and ruled a breach of Clauses 7.2, 7.3 and 7.4.

In relation to the claim in question regarding reduction in potential associated toxicities, the Panel considered that it was not clear in the material what the term 'toxicities' related to. Whilst there was information on bone mineral density and lipid levels below the claim at issue, there was also information about adverse events including psychiatric disorders, nasopharyngitis, headache and diarrhoea to the left of it. In the Panel's view, in the context of this material, the term toxicities could imply any adverse event. The Panel noted its comments at Point B above in relation to lipids; in its view the neutral effect on serum lipids in the dolutegravir/rilpivirine group could not necessarily be considered a reduction in toxicity. The Panel further noted its comments at Point B above regarding the ViiV exchange website and the word 'associated'; it implied that the claimed potential reduction in toxicities was as a direct result of the claimed reduced ARV exposure. However, as previously noted above, it appeared to the Panel that the nature of the medicines in the regimen was a fundamental factor in relation to the effects on, *inter alia*, bone.

The Panel noted its comments at Point A above in relation to adverse events in the SWORD studies. In the Panel's view, the claim regarding reduction in potential associated toxicities could not be substantiated by the SWORD studies.

In the Panel's view, the implication in the claim 'a 2- drug regimen may reduce ARV exposure and potential associated toxicities' that a two-medicine regimen might reduce potential associated toxicities versus a three-medicine regimen was ambiguous, unsubstantiated, did not reflect the available information about adverse events and was a misleading comparison. Breaches of Clauses 7.2, 7.3, 7.4 and 7.9 were ruled.

2 Progress with less

Gilead complained about the following statements: 'For your virologically suppressed patients, PROGRESS WITH LESS (Juluca leavepiece (ref UK/DTGRP/0006/18)) and 'PROGRESS WITH LESS' (Juluca advertisement (ref ViiV/DTGRP/0002/17(1)a)).

ViiV agreed during inter-company dialogue with Gilead to withdraw a journal detachable sleeve (ref ViiV/DTGRP/0002/17b(1)c) in relation to the statement 'progress with less' and therefore that material in relation to the claim 'Progress with less'

was not considered by the Panel. There was no evidence that ViiV had agreed to stop using the claim elsewhere and thus the complaint in relation to the above material proceeded in the usual way.

COMPLAINT

Gilead submitted that in the claims at issue 'less' was not defined, was a hanging comparison and the claim, on its own and in the context in which it was used, implied that switching to Juluca was 'progressive', or an 'upgrade' and that a 2- medicine combination represented progress over a standard triple therapy ARV regimen. This impression was misleading, ambiguous and not capable of substantiation. Further, it created an unbalanced view that there were no risks attached to taking 'less'. Gilead alleged breaches of Clauses 7.2, 7.3, 7.4 and 7.10.

In relation to substantiation, the clinical study data (the SWORD studies) supporting the marketing authorisation for Juluca showed only non-inferior efficacy to the comparator regimens and did so in a very specific setting, with more adverse events for the advertised two-medicine combination than the standard of care comparator.

RESPONSE

ViiV stated that Juluca was a new approach to treatment in HIV in two important aspects. Firstly, it comprised of only two ARVs rather than the standard three, and secondly it was only for use as a maintenance treatment, not for the initial suppression of the virus. Use of the phrase 'Progress with less' conveyed the message that the treatment journey had begun and the use of Juluca was not for initial therapy, but for maintenance treatment after at least six months of suppression. It also reflected the continual evolution of HIV treatment as progress, with Juluca being the first licensed two-medicine regimen to have shown non-inferiority to traditional three medicine regimens, and the first licensed 'maintenance-only' HIV treatment.

In both the leavepiece and the advertisement in question, the phrase was introduced with 'For your virologically suppressed patients' making it clear that Juluca was not for initial treatment, but for those already on their treatment journey. In the advertisement, the first bullet point immediately beneath 'Progress with less' was 'The first single-pill, 2-drug regimen powered by dolutegravir at the core' which made it clear to the target audience of HIV specialists that the 'less' referred to fewer ARVs than in any other complete regimen. The leavepiece had a large picture of the tablet making clear it contained only two ARVs and went into much greater detail about the SWORD studies reinforcing the fact that Juluca was a complete regimen that contained fewer ARVs than any other.

ViiV refuted Gilead's assertion that 'Progress with less' '... created an unbalanced view that there were no risks attached to taking 'less'. There was no implication that there were no side-effects or risks to using Juluca. The advertisement and

leavepiece made it clear that efficacy was no better than traditional triple therapy, all of which had a well-recognized risk of failure and contained the prescribing information with all the requisite contraindications, precautions and side-effects. The leavepiece went into more detail discussing the virological non-response data and adverse events seen in the SWORD studies, and also contained the obligatory prescribing information. ViiV denied any breach of Clauses 7.2, 7.3, 7.4 and 7.10.

PANEL RULING

The Panel noted Gilead's allegation that two statements in two identified materials were in breach of the Code. The Panel considered that each statement in the context of each material identified by Gilead should be considered separately.

A For your virologically suppressed patients, PROGRESS WITH LESS (Juluca leavepiece (ref UK/DTGRP/0006/18))

The Panel noted that the statement appeared on the front page of the A5 bi-folded leavepiece. 'Progress with less' was in large capital letters near the top of the leavepiece and directly above it, in smaller less prominent font, was the statement, 'For your virologically suppressed HIV patients'. Below the statement was a picture of a large rucksack next to a bench and a man walking away from the bench holding a smaller rucksack. Below the picture was the statement 'A new era of HIV treatment starts today'. At the bottom of the page was Juluca's logo, licensed indication and a picture of a tablet with 'dolutegravir' on the left and 'rilpivirine' on the right and the caveat that the tablet was not to exact size.

The Panel noted that Juluca was indicated in adults who had been virologically suppressed on a stable regimen for at least 6 months. The Panel noted that the licensed indication was difficult to read; the font size was small and dark green in colour, set against a light green background. However, the Panel considered that the claim at issue made it clear that Juluca was not for initial therapy.

The Panel noted Gilead's submission that 'less' was a hanging comparison. The Panel noted that although the page made it clear that Juluca was a two-medicine regimen, it was not made clear what Juluca was 'less' than. Only when the leavepiece was opened would the reader see information regarding the SWORD studies and that Juluca was compared to 3-drug regimens. In the Panel's view, the reader should not have to turn a page to see the qualification to a claim. This was particularly so when considering the main claim on the front page of a leavepiece.

The statement 'A new era of HIV treatment starts today', which featured below the picture, implied that there was a comparison being made between Juluca and another HIV treatment. In the Panel's view, it was not clear exactly which HIV treatment Juluca was being compared to in the claim 'Progress with less'. Furthermore, the term 'progress' when read in conjunction with the phrase 'new era' could imply

some level of improvement versus the comparator, which was not supported by the SWORD studies which showed non-inferiority of Juluca compared to continued triple therapy.

Noting its comment above, in the Panel's view the claim 'For your virologically suppressed patients, PROGRESS WITH LESS' was ambiguous, a misleading comparison of Juluca with other HIV treatment and was not capable of substantiation, as alleged, and breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

The Panel noted Gilead's allegation that the claim created an unbalanced view that there were no risks attached to taking 'less'. The Panel noted that it was unclear what risks Gilead was referring to. The Panel noted ViiV's submission that there was no implication that there were no side-effects or risks to using Juluca and that the leavepiece made it clear that efficacy was no better than traditional triple therapy, all of which had a well-recognized risk of failure. The Panel considered that Gilead had not proved, on the balance of probabilities, that the claim in question created an unbalanced view that there were no risks to taking 'less' and ruled no breach of Clause 7.10.

B 'PROGRESS WITH LESS' (Juluca advertisement (ref ViiV/DTGRP/0002/17(1)a))

The Panel noted that the journal advertisement had the same picture as described above at Point 2A. 'Progress with less' was in large capital letters near the top of the advertisement. Directly above it, in smaller less prominent font, was the statement, 'For your virologically suppressed HIV patients'. Below 'Progress with less' were two bullet points which stated, 'The first single-pill, 2-drug regimen powered by dolutegravir at the core' and 'Treatment non-inferior to traditional 3-drug regimens at maintaining virological suppression at 48 weeks'. The advertisement also featured Juluca's logo with the statement 'A new era of HIV treatment starts today'. Juluca's indication was stated along with the statement 'DTG [dolutegravir] 50 mg + RPV [rilpivirine] 25 mg (bioequivalent to JULUCA) used in SWORD studies'.

The Panel noted that, unlike the claim at Point 2A above, the bullet points qualified that 'less' was in relation to a 2 medicine-regimen versus a 3 medicine-regimen.

Whilst the Panel noted the differences between the advertisement in question and the claim in the leavepiece at Point 2A, the Panel still considered that the word 'progress' was ambiguous and misleading. The word could imply advancement of some sort and, in the Panel's view, the claim was a misleading and an unsubstantiated comparison of Juluca compared with triple therapy. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

The Panel considered that Gilead had not proved, on the balance of probabilities, that the claim 'PROGRESS WITH LESS' created an unbalanced view that there were no risks to taking 'less' as alleged and no breach of Clause 7.10 was ruled.

3 2 well-tolerated agents

Gilead complained about the following claims: 'is now available with just 2 well tolerated agents' (Juluca leavepiece (ref UK/DTGRP/0006/18)) and '2 well-tolerated agents, in 1 pill' (Juluca Fast Facts – ViiV exchange website (ref UK/DTGRP/0005/18)).

COMPLAINT

Gilead alleged that the claims were misleading in breach of Clause 7.2 as they placed undue emphasis on the safety profile of the individual components of the Juluca two medicine regimen without clarifying the safety profile of the medicine being promoted.

Gilead submitted that claims about tolerability must be clear and unambiguous and characterised appropriately, must include the use of appropriate substantiating data in a balanced fashion, while also citing the most up-to-date information to support the claims, including reference to the most appropriate summary of product characteristics (SPC).

As identified above, the SWORD study demonstrated that more participants who switched to the Juluca two medicine regimen (17 (3%)) reported adverse events leading to withdrawal than did participants who took triple therapy (3 (<1%)).

Table 3 of Section 5.1 of the Juluca SPC outlined that nearly 6 times as many patients discontinued study/study medicine (Juluca) due to adverse event or death (n=17) vs comparator (n=3); this critical information was absent from the respective component SPCs referenced against this claim, which did not report the clinical experience of combining these individual agents. Table 14, Section K-18 of the DHHS March 2018 guidelines, a leading source of guidelines for the treatment of HIV, identified that nervous system/psychiatric effects were common with both rilpivirine and dolutegravir.

Therefore, it was critical for the intended audience to be able to assess the appropriate frequency of these adverse events when combining these agents in a 2 medicine regimen and they should always be directed to the most relevant up-to-date information – the Juluca SPC.

Gilead alleged that the claims were misleading in breach of Clause 7.2.

RESPONSE

ViiV did not consider that the claims were ambiguous, that they misled, or misrepresented the data as alleged; the company thus denied a breach of Clause 7.2. The SWORD 1 and 2 studies were themselves conducted using the separate licensed agent rilpivirine and dolutegravir as opposed to the fixed dose combination. Hence referring to the separate agents did not misrepresent the study or the data. Furthermore, the above materials all cited adverse event information; total numbers of adverse events; medicine related discontinuations and adverse events occurring in 5% or more of individuals reported in the SWORD studies. ViiV stated that it had ensured that its promotional

material would not be inconsistent with the licence by reminding readers that Juluca, although a new product and new way of treating virologically suppressed patients, was comprised of two ARVs with which they were familiar. This was consistent with the Code which required that all claims were capable of substantiation and that references were supplied promptly if requested.

There was no 'undue emphasis' on the safety profile of individual components as these also reflected the Juluca SPC as Gilead acknowledged in inter-company dialogue on 8 August. Similarly, the authors of the SWORD 1 and 2 studies publication stated 'No new or signature drug-related adverse events were observed with this combined therapy that were not already recognised with the use of the individual components, and no increase was seen in overall frequency or severity of drug-related adverse events. This absence of additive adverse reactions was not surprising given the lack of drug interaction between dolutegravir and rilpivirine'.

Gilead acknowledged in inter-company dialogue that the nature and frequency of adverse events in Section 4.8, of the Juluca SPC was consistent with the SPCs of the individual components. Section 5.1 of an SPC provided contextualizing information about the studies on which the licence was based and would be taken in to account by the regulators when approving an SPC. Had the regulators considered that the information in the adverse event table of Section 4.8 should be amended to differentiate the Juluca adverse event profile from its components, they would have required those changes to be included in Section 4.8. Gilead asserted concerns over nervous system/psychiatric effects and a greater number of adverse events leading to withdrawal, but the EPAR made clear 'No relevant new safety concerns ... were identified as a result of the special monitoring. The psychiatric AE profile (including depression and suicidality) for dolutegravir and rilpivirine was comparable to the known safety profile for the single entities' and 'Based on all safety data submitted it was reasonable to conclude that the safety profile of the combined administration of dolutegravir and rilpivirine seemed to be consistent with the established safety profiles and the current labelling of the single agents. No additional risks or safety issues were identified'. Thus, it appeared that when the data were fully interrogated by the regulators, they did not see the need to amend the Juluca SPC to differ from the individual components in terms of adverse events.

ViiV noted that all of the materials included the Juluca prescribing information as mandated which had the obligatory direction to the Juluca SPC for further information on side-effects. As such the material was not misleading and was in line with the Code. ViiV denied a breach of Clause 7.2.

PANEL RULING

The Panel noted Gilead's allegation that two statements in two identified materials were in breach of the Code. The Panel considered each statement in the context of the material identified by Gilead.

A 'is now available with just 2 well tolerated agents' (Juluca leavepiece (ref UK/DTGRP/0006/18))

The Panel noted that the claim at issue appeared on the back page, which appeared to be the final page of the bi-folded A5 leavepiece. As noted above in Point 1 A, there were three statements, in numerical descending bullet points: 'Juluca is non-inferior to 3-drug regimens at maintaining virological suppression ...', 'is now available with just 2-well-tolerated agents ...', 'all in 1 small pill'.

The Panel noted Gilead's allegation that the claim placed undue emphasis on the safety profile of the individual components of Juluca without clarifying the safety profile of the medicine being promoted and that the audience should be directed to the Juluca SPC.

The Panel noted that the claim at issue 'is now available with just 2 well tolerated agents' was referenced to the dolutegravir and rilpivirine individual SPCs and not the Juluca SPC, however, the Juluca SPC was also included in the list of references.

The Panel noted that ViiV's submission quoted the European Public Assessment report and stated 'Based on all safety data submitted it is reasonable to conclude that the safety profile of the combined administration of DTG [dolutegravir] and RPV [rilpivirine] seems to be consistent with the established safety profiles and the current labelling of the single agents. No additional risks or safety issues were identified'.

The Panel noted ViiV's submission that the SWORD studies were conducted using the separate licensed agents, dolutegravir and rilpivirine, as opposed to the fixed dose combination and that the Juluca European Medicines Agency (EMA) licence was underpinned by the SWORD 1 and 2 studies.

The Panel noted that page 3 of the leavepiece detailed safety results from the SWORD studies including the rates of adverse events, drug-related adverse-events resulting in discontinuation (Juluca 4% vs continued 3-drug regimens <1%), and adverse events reported in $\geq 5\%$ of subjects in the Juluca arm (psychiatric disorders 12%, nasopharyngitis 10%, headache 8% and diarrhoea 6%). Page 3 of the leavepiece also stated that in studies supporting Juluca, dolutegravir 50mg and rilpivirine 25mg were used and that bioequivalence with Juluca had been demonstrated. The Panel noted that nonetheless the claim should be capable of standing alone.

The Panel noted its comments above and did not consider that the claim at issue 'is now available with just 2 well tolerated agents' in the context of the leavepiece was misleading by virtue of the emphasis on the individual components without clarifying the safety profile of Juluca, as alleged. No breach of Clause 7.2 was ruled.

B '2 well-tolerated agents, in 1 pill' (Juluca Fast Facts – ViiV exchange website (ref UK/DTGRP/0005/18))

The Panel noted its description of this material in Point 1D above. The Fast Facts sheet referred to the SWORD studies including: design, the rates of adverse events in the two treatment arms, rates of drug-related adverse events resulting in discontinuation, adverse events reported in $\geq 5\%$ of subjects in the Juluca arm and that bioequivalence of Juluca to dolutegravir 50mg and rilpivirine 25mg had been demonstrated.

The Panel noted its comments above at Point 3A. The Panel did not consider that the claim '2 well-tolerated agents, in 1 pill' in the context of the material was misleading by virtue of the emphasis on the individual components without clarifying the safety profile of Juluca, as alleged. No breach of Clause 7.2 was ruled.

4 Size of tablet claim

Gilead complained about the claim 'All in 1 small pill' (Juluca leavepiece (ref UK/DTGRP/0006/18)).

COMPLAINT

Gilead submitted that the claim was ambiguous as it did not clarify the actual dimensions of the Juluca tablet. Without this clarification Gilead also considered the claim was a hanging comparison, as it was unclear to the reader in comparison to what the tablet was considered small. Gilead alleged a breach of Clause 7.2.

RESPONSE

ViiV did not consider that the claim was a hanging comparison, and therefore it denied a breach of Clause 7.2. 'Smaller' or 'smallest' without qualification would be, but 'small' was not comparative but an objective statement of fact. The dimensions of Juluca (14 x 7mm) substantiated the claim of 'small' and, although no comparison was made in the material, it was the smallest complete single-pill HIV regimen. By any standards, ViiV believed Juluca was small even when compared with what would be regarded as 'small'; in a study looking at the most commonly prescribed paediatric medications and their sizes, the dimensions of Juluca were comparably on the smaller spectrum of medications available for children (Jacobson *et al* 2016).

PANEL RULING

The Panel noted that the claim at issue featured on the back page of the bi-folded A5 leavepiece. The Panel noted that the dimensions of Juluca, as stated in the SPC, were 14 x 7mm. The Panel noted ViiV's submission that Juluca was the smallest complete single-pill HIV regimen. The Panel further noted that ViiV referred to a study by Jacobson *et al* (2016) on the sizes of commonly prescribed paediatric medicines; ViiV submitted that Juluca was comparably on the smaller spectrum of medicines available for children. The Panel noted that Jacobson *et al* stated that common paediatric antibiotics ranged from 8 to 25mm in length, median 17mm. The Panel further noted that Juluca was indicated for use in adults only.

In the Panel's view, the description 'small' was somewhat subjective, however, the Panel did not consider that the claim was ambiguous by not stating the dimensions, as alleged. The audience was an important consideration and the Panel considered whether the description would be misleading to HIV physicians. Noting its comments above, the Panel did not consider that the claim 'All in one small pill' was a hanging comparison or that Gilead had proved, on the balance of probabilities, that the description would be misleading to the intended audience. No breach of Clause 7.2 was ruled.

5 High standards

COMPLAINT

Gilead submitted that, generally, in relation to all of the above issues, ViiV had failed to maintain high standards, in breach of Clause 9.1.

RESPONSE

Overall ViiV strongly disputed the alleged breaches and a breach of Clause 9.1.

PANEL RULING

The Panel noted its comments and rulings of breaches of the Code at Points 1 and 2 above. In the Panel's view, ViiV had failed to maintain high standards and a breach of Clause 9.1 was ruled.

Complaint received	7 September 2018
Case completed	15 August 2019