ANONYMOUS GENERAL PRACTITIONER v ViiV HEALTHCARE

Promotion of Triumeq

An anonymous general practitioner complained about a Triumeq advertisement issued by ViiV Healthcare UK and published in the BMJ. Triumeq was a fixed dose combination of dolutegravir, abacavir and lamivudine as a single-tablet for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents above 12 years of age who weighed at least 40kg.

The advertisement featured the claim 'inner strength. The only single-pill regimen built with dolutegravir' above the claim 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks'. The claim was referenced, *inter alia*, to Walmsley *et al* (2013, the SINGLE study). The asterisk referred to a footnote 'In studies supporting Triumeq, [dolutegravir 50mg + abacavir 600mg/ lamivudine 300mg] were used. Bioequivalence has been demonstrated. Atripla is not licensed for initial use in treatment-naïve patients'.

The complainant alleged that 'inner strength' implied a panacea against all ills. He also considered it was unfair to compare Truimeq against Atripla outside its licensed indication and queried whether the studies cited actually used the fixed dose combination or just the individual components.

The detailed response from ViiV Healthcare is given below.

The Panel noted that 'inner strength' had the largest font size within the advertisement and was in Triumeq branded colours, directly above the less prominent claim 'The only single-pill regimen built with dolutegravir'. The first part of the claim beneath this began 'The components of Triumeq form the first HIV regimen…'. The Panel considered that it was clear from the advertisement that Triumeq was for the treatment of HIV and thus that 'inner strength' did not imply that the medicine was a panacea for all ills as alleged. No breach of the Code was ruled.

The Panel noted the allegation that it was unfair to compare Truimeq with Atripla outside its licensed indication and considered that in this regard the complainant had referred to the use of Atripla (marketed by Gilead Sciences) outside of its licensed indication although the construction of the relevant sentence in the complaint was such that this was not entirely clear. The Panel noted that ViiV Healthcare had responded on this basis.

The claim 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks', was referenced, *inter alia*, to Walmsley *et al*. The associated footnote stated, *inter alia*, that Atripla was not licensed for initial use in treatment-naïve patients. Walmsley *et al* was one of the Phase III studies upon which the licence for Triumeq had been granted. The double-blind study compared the safety and efficacy of Triumeq (as dolutegravir plus abacavir/ lamivudine ie two tablets) with that of Atripla administered as a single tablet. The patients had not previously received therapy for HIV infection. When the SINGLE study was conducted, Atripla was the only single-tablet regimen preferred in the US HIV treatment guidelines and one of the two recommended single-tablet regimens in the European treatment guidelines.

The Panel noted that Atripla was a once daily fixed dose combination indicated for the treatment of HIV infection. The SPC stated that 'No data are currently available from clinical studies with Atripla in treatment-naïve or in heavily pre-treated patients'.

The Panel noted the complainant's allegation that it was unfair to compare Triumeq with Atripla outside its licensed indication ie because Atripla had been used as initial therapy in HIV patients. The Panel considered that this was a difficult matter. The Code was clear that the promotion of a medicine must be in accordance with its marketing authorization and not be inconsistent with the particulars listed in its SPC. The company was not promoting a competitor medicine and so in that regard the Panel ruled no breach of the Code.

The Panel questioned whether comparing products using an unlicensed dose or treatment regimen of a competitor met the requirements of the Code. Readers might be misled as to the approved use of the competitor product and the company that marketed the competitor product might not be able to use or counter those claims as it might be accused of promoting an unlicensed dose etc. The Panel noted that the claim in question clearly stated that Atripla had been used in treatment-naïve patients. An asterisk next to the mention of Triumeq, rather than Atripla or the reference to treatment-naïve patients, led readers to a footnote, the third sentence of which stated that Atripla was not licensed for initial use in treatment-naïve patients; this appeared to be an acknowledgement from ViiV Healthcare that Atripla had been used outside of its licensed indication. The Panel noted that the supplementary information to the Code stated that claims must be capable of standing alone and that, in general, they should not be qualified by the use of footnotes. The Panel considered that

the claim at issue could not standalone without misleading readers as to the licensed indication for Atripla and on this very narrow point, the Panel ruled a breach of the Code. This ruling was appealed by ViiV Healthcare.

The Appeal Board noted ViiV Healthcare's submission that Atripla was a well accepted first-line treatment for HIV in the UK albeit that it was not licensed for use in treatment-naïve patients and that, given current clinical practice worldwide, Atripla had been accepted as the appropriate comparator in Walmsley *et al* which was cited in the Triumeq summary of product characteristics (SPC). In addition the use of Atripla in treatment-naïve patients was supported by independent treatment guidelines and the medicine was licensed for such use in the US.

The Appeal Board noted that HIV was a highly specialised therapy area. The SPCs for Triumeq and Atripla stated that the medicines had to be respectively 'prescribed' or 'initiated' by physicians 'experienced in the management of HIV infection'. ViiV Healthcare stated that there were currently approximately 800 such physicians in the UK. The Appeal Board considered that such a specialised audience was likely to prescribe medicines off-licence. The Appeal Board noted ViiV Healthcare's submission that such physicians would be familiar with the Atripla licence and would know that first-line use of the medicine had not been approved in the UK.

The Appeal Board noted its comments above and that the advertisement appeared only in the hospital edition of the BMJ. It therefore considered that the claim in question 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks' reflected current clinical practice and in that regard patients were not put at risk. The Appeal Board considered that given the particular set of circumstances and factors discussed above, the claim at issue was not misleading and on this narrow point it ruled no breach of the Code. The appeal was successful.

The Panel noted the complainant queried whether the studies cited had used the fixed dose combination or the individual components. The claim explicitly referred to 'The components of Triumeq…' and to the use of Atripla and not to the use of its components. The Panel considered that the complainant appeared to understand that Atripla as a fixed dose combination had been used. The Panel considered that it was sufficiently clear from the advertisement that Triumeq had been administered as its components and that Atripla had been administered as the single fixed dose tablet and so in that regard the advertisement was not misleading. No breach of the Code was ruled.

An anonymous General Practitioner complained about a Triumeq advertisement (UK/TRIM/0022/14A) issued by ViiV Healthcare UK Limited and published in the BMJ, 14 March 2015. Triumeq was a fixed dose combination of dolutegravir, abacavir and lamivudine as a single-tablet regimen for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents above 12 years of age who weighed at least 40kg.

The top three quarters of the double-page spread advertisement consisted of a visual on the left and narrative on the right-hand side; the prescribing information and other obligatory information occupied the lower quarter of the advertisement. The advertisement featured the claim 'inner strength. The only single-pill regimen built with dolutegravir' above the claim 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks'. The claim was referenced to Walmsley *et al* (2013, the SINGLE study), Walmsley *et al* (2014) and Pappa *et al* (2014). The asterisk directed readers to the footnote 'In studies supporting Triumeq, [dolutegravir 50mg + abacavir 600mg/lamivudine 300mg] were used. Bioequivalence has been demonstrated. Atripla is not licensed for initial use in treatment-naïve patients'.

COMPLAINT

The complainant alleged that 'inner strength' implied a panacea against all ills. He also considered it was unfair to compare Truimeq against Atripla outside its licensed indication and queried whether the studies cited actually used the fixed dose combination (FDC) or just the individual components.

When writing to ViiV Healthcare, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2 of the 2014 Code.

RESPONSE

ViiV Healthcare stated that it was committed to complying with the Code and stated that its medical and commercial signatories were registered in accordance with Clause 14.4.

1 'inner strength'

ViiV Healthcare did not consider that the advertisement at issue implied a panacea against all ills. The Oxford dictionary defined panacea as 'a solution or remedy for all difficulties or diseases'. Individuals would interpret an advertisement in their own way but it was stated in the text immediately below that Triumeq was the 'first HIV regimen....' and ViiV Healthcare thus submitted that it was clear that the advertisement related to HIV only and that it was not ambiguous or misleading as a potential treatment for any other disease, condition or illness. There was no breach of Clause 7.2.

2 Comparison with Atripla

ViiV Healthcare noted that Atripla was the first single-tablet regimen to become available in December 2007; it gave patients a simple and more convenient way of treating their HIV with three established antiretroviral agents. The European AIDS Clinical Society (EACS) Guidelines recommended two

nucleos(t)ides with either a non-nucleoside, boosted protease inhibitor or integrase inhibitor; furthermore the guidelines specifically recommended, when appropriate, that the components of Atripla be given as the single-tablet in HIV treatment-naïve patients. Given the success of this co-formulation, recently approved HIV single-tablet regimens had compared themselves with Atripla as a gold standard; this included Triumeq and Stribild, licensed in May 2013. ViiV Healthcare submitted that the comparison of Triumeq with Atripla in the SINGLE study was appropriate and reflected clinical practice. To enable prescribers to make an informed clinical decision ViiV Healthcare believed it was important to communicate the results of the SINGLE study, whereby Triumeq was superior to Atripla.

Furthermore, the advertisement focussed on Triumeq and communicated the results of the SINGLE study and therefore could not be deemed to promote another company's product. As Triumeq was licensed for the treatment of HIV infected adults and adolescents above 12 years of age weighing at least 40kg, ViiV Healthcare submitted that the advertisement was not in breach of Clause 3.2.

3 Fixed dose combination or individual components?

ViiV Healthcare noted that the advertisement explicitly stated that 'In studies supporting Triumeq, [dolutegravir with abacavir/lamivudine] were used. Bioequivalence has been demonstrated'.

The European Medicines Agency (EMA) approved Triumeq based on the clinical trial data from three large Phase III studies (Walmsley *et al* (SINGLE), Raffi *et al* 2013 (SPRING-2) and Clotet *et al* 2014 (FLAMINGO)) and the results of a bioequivalence study (Weller *et al* 2014). ViiV Healthcare submitted that the advertisement was consistent with Clause 7.2 given that the information was based on the Triumeq summary of product characteristics (SPC) dated September 2014.

Summary

ViiV Healthcare did not consider that the advertisement was misleading or ambiguous or that it promoted outside the Triumeq licence and as such did not breach Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted that the complainant's allegation that the claim 'inner strength' implied that Triumeq was a panacea for all ills. The Panel noted that 'inner strength' had the largest font size within the advertisement and was in Triumeq branded colours, directly above the less prominent claim 'The only single-pill regimen built with dolutegravir'. The first part of the claim beneath this began 'The components of Triumeq form the first HIV regimen…'. The Panel considered that it was clear from the advertisement that Triumeq was for the treatment of HIV and thus the claim in question, 'inner strength', did not imply that the medicine was a panacea for all ills as alleged. There was no direct or indirect reference to any other medical condition. No breach of Clause 7.2 was ruled.

The Panel noted the allegation that it was unfair to compare Truimeq with Atripla outside its licensed indication and considered that in this regard the complainant had referred to the use of Atripla (marketed by Gilead Sciences) outside of its licensed indication although the construction of the relevant sentence in the complaint was such that this was not entirely clear. The Panel noted that ViiV Healthcare had responded on this basis.

The claim 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks', was referenced, *inter alia*, to Walmsley *et al*. The asterisk led to a footnote which stated, *inter alia*, that Atripla was not licensed for initial use in treatment-naïve patients. Walmsley *et al* was one of the Phase III studies upon which the licence for Triumeq had been granted. The study compared the safety and efficacy of Triumeq (as dolutegravir plus abacavir/lamivudine ie two tablets) with that of Atripla administered as a single tablet (placebo tablets were used to double-blind the study and all patients received three tablets a day). The patients had not previously received therapy for HIV infection. The investigators noted that when they conducted the SINGLE study, the comparator, Atripla, was the only single-tablet regimen preferred in the US HIV treatment guidelines and it was also one of the two recommended single-tablet regimens in the European treatment guidelines.

The Panel noted that Atripla was a once daily fixed dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate which according to its SPC was 'indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Atripla prior to initiation of their first antiretroviral treatment regimen'. The SPC also stated, *inter alia*, that 'No data are currently available from clinical studies with Atripla in treatment-naïve or in heavily pre-treated patients'.

The Panel noted the complainant's allegation that it was unfair to compare Triumeq with Atripla outside its licensed indication ie because Atripla had been used as initial therapy in HIV patients. The Panel considered that this was a difficult matter. Clause 3 of the Code was clear that the promotion of a medicine must be in accordance with its marketing authorization and not be inconsistent with the particulars listed in its SPC. A company would not be promoting a competitor medicine and so in that regard the Panel considered that Clause 3 would not apply and so it ruled no breach of Clause 3.2.

Clause 7.2 of the Code required that information, claims and comparisons be accurate balanced, fair, objective, unambiguous and based on an up-to-

date evaluation of all the evidence and reflect that evidence clearly. Claims must not mislead either directly or by implication. The Panel questioned whether comparing products using an unlicensed dose or treatment regimen of a competitor met the requirements of Clause 7.2. Readers might be misled as to the approved use of the competitor product and the company that marketed the competitor product might not be able to use or counter those claims as it might be open to accusations of promoting an unlicensed dose etc. The Panel noted that the claim in question clearly stated that Atripla had been used in treatment-naïve patients. An asterisk next to the mention of Triumeq, rather than Atripla or the reference to treatment-naïve patients, led readers to a footnote, the third sentence of which stated that Atripla was not licensed for initial use in treatment-naïve patients; this appeared to be an acknowledgement from ViiV Healthcare that Atripla had been used outside of its licensed indication. The Panel noted that the supplementary information to Clause 7 stated that claims must be capable of standing alone and that, in general, they should not be qualified by the use of footnotes. The Panel considered that the claim at issue could not standalone without misleading readers as to the licensed indication for Atripla and on this very narrow point, the Panel ruled a breach of Clause 7.2. This ruling was appealed.

The Panel noted the complainant queried whether the studies cited had used the fixed dose combination or just the individual components. The Panel noted that the central claim explicitly referred to 'The components of Triumeq…' and to the use of Atripla and not to the use of its components. The Panel considered that given the complainant's concerns about the comparison of Triumeq with Atripla, he had appeared to understand that Atripla as a fixed dose combination had been used. The Panel considered that it was sufficiently clear from the advertisement that Triumeq had been administered as its components and that Atripla had been administered as the single fixed dose tablet and so in that regard the advertisement was not misleading. No breach of Clause 7.2 was ruled.

APPEAL BY VIIV HEALTHCARE

ViiV Healthcare noted that the Panel had ruled a breach of Clause 7.2 on the very narrow point that the claim could not stand alone without misleading the readers as to the licensed indication of Atripla. ViiV Healthcare submitted that UK HIV physicians would not be misled by the claim at issue as they were extremely familiar with Atripla and had used it as an initial regimen for the treatment of HIV for nearly eight years.

ViiV Healthcare stated that its appeal against the Panel's ruling was based on four interlinked elements:

1 HIV treatment regimens must be prescribed by expert physicians only

ViiV Healthcare noted that both the Triumeq and Atripla SPCs stated that treatment should be initiated by a physician experienced in the management of HIV infection and thus the audience for this advertisement were experts in the field of HIV. Those who were not HIV experts should not initiate treatment.

ViiV Healthcare noted that the advertisement was placed in the hospital edition of the BMJ, which reached over 70,000 hospital doctors in the UK who were members of the BMA. The journal was chosen as it was read by approximately 52% of senior infectious disease specialists in the UK. The advertisement did not appear in the version of the BMJ which was sent to GPs only.

2 Atripla was well known to the HIV expert audience and known to be prescribed as initial HIV treatment

ViiV Healthcare noted that the components of Atripla had been licensed for initial treatment of HIV in the UK for over a decade: efavirenz (EFV) in 1999, tenofovir disoproxil fumarate (TDF) in 2002 and emtricitabine (FTC) in 2003; the fixed dose combination of FTC/TDF was licensed in 2005. (Sastiva, Viread and Emtrivia SPCs). ViiV Healthcare submitted that HIV physicians were very familiar with the combination of EFV/TDF/FTC and the three components had been recommended as a preferred initial regimen by the British HIV Association (BHIVA) since 2005 (BHIVA Guidelines 2005 and 2014).

ViiV Healthcare noted that the first single tablet regimen, Atripla (EFV/TDF/FTC), was licensed in Europe in 2007 and established itself as the standard of care for treatment-naïve patients with HIV in the UK despite its licensed indication requiring initial suppression by another regimen. ViiV Healthcare submitted that it must be mindful that prescribers were not bound by licensed indications and could prescribe any treatment for any condition if they considered it was in the best interests of their patients and were prepared to justify that decision if need be; this was endorsed by treatment guidelines which highlighted the importance of individualising therapy (BHIVA Guidelines 2014, EACS Guidelines (version 7.1), November 2014, International AntiViral Society (IAS) USA Guidelines 2014, Department of Health and Human Services (DHHS) Guidelines, April 2015).

ViiV Healthcare provided a letter dated 1 May 2015 from an HIV specialist which verified that HIV physicians in the UK clearly considered there was adequate evidence of the efficacy and safety of using Atripla in this way, as did the US regulators where it was licensed for initial treatment (Atripla US prescribing information (January 2015). Current practice supported the use of Atripla outside the terms of its UK licence as it was still the most commonly used first-line regimen for HIV in the UK, with nearly eight years' experience. Thus it was clear that UK HIV physicians were extremely familiar with Atripla and would not be misled by the claim at issue or need any further information to enable them to understand the relevance of the claim to their clinical practice.

3 Atripla was used as the comparator arm in treatment-naïve studies as the current standard of care

ViiV Healthcare submitted that the EMA acknowledged and accepted Atripla as the appropriate comparator in the registrational trial, SINGLE, which was used to support regulatory submissions for both Tivicay and Triumeq (Tivicay and Triumeq SPCs); Atripla was also used by Gilead for the Stribild submission (Stribild SPC). All of these medicines used the data from their registration studies in their promotional campaigns. In all of these studies, Atripla was used outside the terms of its European licence as initial therapy and the EMA had accepted the results of these studies and included details of them in the respective SPCs. There were no caveats or qualifications around the use of Atripla as the comparator in the therapy-naïve population in the Triumeq SPC where the SINGLE study was discussed:

> 'The efficacy of Triumeq in HIV-infected, therapy naïve subjects is based on the analyses of data from two randomized, international, double-blind, active-controlled trials, SINGLE (ING114467) and SPRING-2 (ING113086) and the international, open-label, active-controlled trial FLAMINGO (ING114915).'
>
> 'In SINGLE, 833 patients were treated with dolutegravir 50mg once daily plus fixed-dose abacavir-lamivudine (DTG + ABC/3TC) or fixed-dose efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC).'
>
> 'EFV/TDF/FTC = efavirenz 600mg, tenofovir 300mg, emtricitabine 200mg in the form of Atripla FDC.'

Consequently, ViiV Healthcare submitted that as it was important to promote Triumeq appropriately and in a manner wholly consistent with its SPC, the comparison with Atripla from SINGLE was both fair and clinically relevant and reflected current UK practice. ViiV Healthcare submitted that if it was unable to include balanced and objective references to Atripla (as an acceptable comparator arm) in dolutegravir's key registration study, it would restrict communication of critical information about HIV medicines to health professionals; this could indirectly impact health professionals' decision-making, rationale prescribing choices and optimal selection of individual antiretroviral agents thereby reducing the benefits to patients.

4 The claim stood alone and was not qualified by a footnote

ViiV Healthcare noted, as the Panel acknowledged, a company would not promote a competitor product and the claim at issue clearly promoted Triumeq, not Atripla, and the study upon which the claim was based reflected the current use of Atripla in the UK and thus it was a fair comparison and was not misleading.

ViiV Healthcare submitted that the claim related to the superiority of Triumeq over Atripla, a commonly prescribed initial treatment for HIV in the UK. HIV physicians would not be misled as to the approved use of Atripla as this was how they had used it for nearly eight years. However, as this was off-label use of Atripla, a statement to this effect should be included and was added as a final line in the advertisement to ensure transparency. It did not qualify the claim, but acknowledged the licence status of Atripla; not to do so could be considered misleading.

COMMENTS FROM THE COMPLAINANT

There were no comments from the complainant.

APPEAL BOARD RULING

The Appeal Board noted ViiV Healthcare's submission that Atripla was a well accepted first-line treatment for HIV in the UK albeit that it was not licensed for use in treatment-naïve patients and that, given current clinical practice worldwide, Atripla had been accepted as the appropriate comparator in the Phase III pivotal, SINGLE study (Walmsley *et al*). The SINGLE study was cited in the Triumeq SPC. In addition the use of Atripla in treatment-naïve patients was supported by independent treatment guidelines and the medicine was licensed for such use in the US.

The Appeal Board noted that HIV was a highly specialised therapy area. The SPCs for Triumeq and Atripla stated that the medicines had to be respectively 'prescribed' or 'initiated' by physicians 'experienced in the management of HIV infection'. In response to a question the representatives from ViiV Healthcare stated that there were currently approximately 800 such physicians in the UK. The Appeal Board considered that such a specialised audience was likely to prescribe medicines off-licence. The Appeal Board noted ViiV Healthcare's submission that such physicians would be familiar with the Atripla licence and would know that first-line use of the medicine had not been approved in the UK.

The Appeal Board noted its comments above and that the advertisement appeared only in the hospital edition of the BMJ. It therefore considered that the claim in question 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks' reflected current clinical practice and in that regard patients were not put at risk. The Appeal Board considered that given the particular set of circumstances and factors discussed above, the claim at issue was not misleading and on this narrow point it ruled no breach of Clause 7.2. The appeal was successful.

Complaint received	**13 March 2015**
Case completed	**17 June 2015**