AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

# AWMSG SECRETARIAT ASSESSMENT REPORT

## Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®) 50 mg/200 mg/25 mg film-coated tablets

Reference number: 3414

## FULL SUBMISSION

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®) 50 mg/200 mg/25 mg film-coated tablets. Reference number: 3414. October 2018.

# AWMSG Secretariat Assessment Report
# Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®▼)
# 50 mg/200 mg/25 mg film-coated tablets

## 1.0 KEY FACTS

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| **Assessment details** | Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®▼) for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.<br><br>▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. |
| **Current clinical practice** | Guidelines recommend that antiretroviral therapy (ART) in treatment-naïve patients with HIV-1 consists of two nucleoside reverse transcriptase inhibitors (NRTIs) plus either integrase inhibitor, ritonavir-boosted protease inhibitor or non-NRTI.<br><br>The company anticipates that Biktarvy® will be used in place of alternative integrase inhibitor-based single tablet regimens, dolutegravir/abacavir/lamivudine (Triumeq®) and elvitegravir/ cobicistat/emtricitabine/tenofovir alafenamide (Genvoya®), as either a first-line therapy or as an alternative treatment option for treatment-experienced patients who need to switch from their existing therapy due to issues relating to efficacy, tolerability or regimen simplification.<br><br>Clinical expert opinion suggests that the comparators are appropriate for this submission; however, there is some uncertainty as to whether the comparators reflect a comprehensive representation of clinical practice in Wales. |
| **Clinical effectiveness** | Data from three phase III studies reported that Biktarvy® was non-inferior to Triumeq® or dolutegravir plus emtricitabine and tenofovir alafenamide (Descovy®) in treatment-naïve patients, and that switching to Biktarvy® was non-inferior to remaining on Triumeq® or staying on baseline regimen in ART-experienced patients, in terms of virological suppression. There was no development of treatment-emergent resistance.<br><br>There is no direct head-to-head data available for Biktarvy® versus Genvoya® so the company conducted a network meta-analysis (NMA) to inform the comparison with Genvoya®. There was considerable between-study heterogeneity and the analysis was of treatment-naïve patients only. Company reported results suggest that the efficacy of Biktarvy® was non-inferior to Triumeq® and Genvoya®. However the NMA is subject to limitations. |

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| **Cost-effectiveness** | A cost minimisation analysis (CMA) compares Biktarvy® with Triumeq® and Genvoya® in the first-line treatment of adults with HIV-1 without any known mutations associated with resistance to the individual components of Biktarvy®.<br><br>The company base case suggests cost savings of [commercial in confidence figure removed] (per patient/annum) when Biktarvy® is compared with Triumeq® and [commercial in confidence figure removed] when compared with Genvoya®. The reported cost savings take into account the current Wales Patient Access Schemes (WPAS) for Biktarvy® and Genvoya® but not the WPAS for Triumeq®. The analyses are therefore not reflective of current cost differences in Wales.<br><br>The use of CMA is inappropriate in this instance, given the absence of well-designed equivalence studies and the differences in safety and patient reported outcomes. The model is also limited to a comparison of acquisition costs only, and choice of comparators is subject to uncertainty. |
| **Budget impact** | The company estimates that 93 patients are eligible to receive treatment with Biktarvy® in Wales in Year 1, increasing to 338 patients in Year 5. The company base case suggests cost savings of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. Further analyses explore the impact of a WPAS when the acquisition cost of Triumeq® is discounted between 5–95%.<br><br>The model is limited to a comparison of acquisition costs only, and the choice of comparators are subject to uncertainty. |

This assessment report is based on evidence submitted by Gilead Sciences Ltd and an evidence search conducted by AWTTC on 9 July 2018[1].

## 2.0 BACKGROUND

### 2.1 Condition and clinical practice

Human immunodeficiency virus (HIV) is a retrovirus that infects and replicates primarily in human $CD4^+$ T cells and macrophages[2]. There are two forms of the virus, HIV-1 and HIV-2, of which HIV-1 is the more virulent and responsible for most of the global pandemic[3]. If left untreated, most people with HIV will develop progressive immunodeficiency marked by $CD4^+$ T lymphocyte cell depletion and leading to AIDS-defining illnesses and premature death[2].

Current guidelines recommend that the antiretroviral therapy (ART) in treatment-naïve people with HIV-1 consists of two NRTIs plus either ritonavir-boosted protease inhibitor, non-NRTI or integrase inhibitor[4]. The British HIV Association guidelines recommend a backbone of either emtricitabine and tenofovir disoproxil (Truvada®) or emtricitabine and tenofovir alafenamide (Descovy®), with abacavir and lamivudine (Kivexa®) as an alternative. These are in combination with ritonavir-boosted atazanavir, ritonavir-boosted darunavir, dolutegravir, raltegravir, elvitegravir/cobicistat or rilpivirine third agents, and alternative third agent efavirenz. In people on suppressive ART regimens, consideration

is given to differences in side-effect profile, interactions between medicines and patterns of resistance to medicines before switching any antiretroviral component[4].

### 2.2 Medicine

Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®) is a fixed dose combination product for once daily administration for the treatment of adults infected with HIV-1 without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir (June 2018)[5]. The applicant company anticipates that Biktarvy® will be used in place of alternative integrase inhibitor-based single tablet regimens as either a first-line therapy or as an alternative treatment option for treatment-experienced patients who need to switch from their existing therapy due to issues relating to efficacy, tolerability or regimen simplification[1].

### 2.3 Comparators

The comparators included in the company's submission are:

- dolutegravir/abacavir/lamivudine (Triumeq®)
- elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya®)

Triumeq® was used as a comparator in the pivotal clinical studies and Genvoya® was used as a comparator in the network meta-analysis (NMA).

### 2.4 Guidance and related advice

- British HIV Association. Guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update)[4].
- National Institute for Health and Care Excellence. Clinical knowledge summaries. HIV infection and AIDS (2015)[6].

The All Wales Medicines Strategy Group (AWMSG) has previously recommended the use of dolutegravir/abacavir/lamivudine (Triumeq®)[7], elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya®)[8] and elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®)[9].

### 2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®) may be supplied by a home healthcare provider.

## 3.0 CLINICAL EFFECTIVENESS

The company submission includes evidence from three pivotal phase III non-inferiority studies in people with HIV[1]. Two are of ART-naïve patients (studies GS-US-380-1489 and GS-US-380-1490), and one is of virologically suppressed patients (study GS-US-380-1844). All three evaluated the efficacy and safety of Biktarvy®, with virological suppression at 48 weeks as the primary outcome. The company submission also included a systematic literature review and NMA to address the lack of direct head-to-head data available for Biktarvy® versus Genvoya® and to reinforce the clinical study data for Triumeq®[1].

### 3.1 Treatment-naïve patients

#### 3.1.1 Study GS-US-380-1489[10]

GS-US-380-1489 was a randomised, double-blind, multicentre, active-controlled study that compared two fixed dose regimens in ART-naïve adults[10]. Patients were randomly assigned (1:1) to one of two treatment groups. A total of 314 patients were treated with Biktarvy® plus placebo-to-match Triumeq® once daily, and 315 were treated with Triumeq® plus placebo-to-match Biktarvy® once daily[2,10]. The use of medications for the treatment of HIV, other than Biktarvy® or Triumeq®, was prohibited[10]. Patients with any known allergies to the excipients of Biktarvy® or Triumeq® were excluded from the study[10].

Table 1 shows the primary endpoint results. A similar proportion of patients had viral suppression (HIV-1 RNA < 50 copies/ml) in the Biktarvy® group, compared with Triumeq® (92.4% versus 93.0%, respectively; −0.6% treatment difference; 95% CI −4.8% to 3.6%; p = 0.78) at week 48[10]. Rates of virological failure were similar for both treatment groups (1.0% versus TRI 2.5%, respectively). No patients discontinued treatment with either Biktarvy® or Triumeq® due to a lack of efficacy[10].

Secondary endpoints, included percentages of patients with plasma HIV-1 RNA < 50 copies/ml and changes from baseline in bone mineral density[10]. Results were consistent with those of the primary analysis. None of the patients developed treatment-emergent resistance to any medicine used in the study[10].

#### 3.1.2 Study GS-US-380-1490[11]

GS-US-380-1490 was a randomised, double-blind, multicentre, active-controlled study that compared Biktarvy® versus dual therapy dolutegravir plus Descovy® in ART-naïve adults[11]. Patients were randomly assigned (1:1) to one of two treatment groups. A total of 320 patients were treated with Biktarvy® and placebo-to-match dolutegravir plus Descovy® once daily; and 325 patients were treated with dual therapy consisting of Descovy® plus dolutegravir plus placebo-to-match Biktarvy® once daily. The use of medications for the treatment of HIV, other than the medicines used in the study, was prohibited. Patients with any known allergies to the excipients of Biktarvy® or dolutegravir were excluded from the study[11].

Table 1 shows the primary endpoint results. A similar proportion of patients had viral suppression (HIV-1 RNA < 50 copies/mL) in the Biktarvy® group, compared with dolutegravir plus Descovy® (89.4% versus 92.9%, respectively; −3.5% treatment difference; 95% CI −7.9% to 1.0%; p = 0.12) at week 48[11]. The rate of virological failure was higher for the Biktarvy® group (4.4% versus dolutegravir plus Descovy® 1.2%, respectively). Eleven participants (3%) discontinued treatment with Biktarvy® due to reasons including being lost to follow-up or having withdrawn consent. No patients discontinued treatment with either Biktarvy® or dolutegravir plus Descovy® due to a lack of efficacy[11].

Secondary endpoints, including percentages of patients with plasma HIV-1 RNA < 50 copies/ml were consistent with those of the primary analysis[1]. None of the patients developed treatment-emergent resistance to any of the medicines used in the study[11].

### 3.2 Virologically suppressed patients

#### 3.2.1 Study GS-US-380-1844[1]

GS-US-380-1844 was a randomised, double-blind, multicentre, active-controlled study that evaluated the switching to Biktarvy® compared with continuing Triumeq® or dolutegravir plus Kivexa® in virologically suppressed, ART-experienced adults[1]. Patients were randomly assigned (1:1) to one of two treatment groups. A total of 282 patients switched to Biktarvy® plus placebo-to-match Triumeq®, and 281 patients remained on Triumeq® plus placebo-to-match Biktarvy®. The use of medication for the treatment of HIV, other than the medicines being studied, was prohibited[1].

Table 1 shows the primary endpoint results. A similar proportion of patients had HIV-1 RNA ≥ 50 copies/ml in the Biktarvy® group, compared with Triumeq® (1.1% versus 0.4%, respectively; 0.7% treatment difference; 95% CI −1.0% to 2.8%; p = 0.62) at week 48[1].

Secondary efficacy endpoint analysis indicated that switching to Biktarvy® and continuing with Triumeq® both achieved a similar viral suppression rate (HIV-1 RNA < 50 copies/ml) at week 48 (93.6% versus 95.0%, respectively; −1.4% treatment difference; 95% CI −5.5% to 2.6%; p = 0.59)[1]. Secondary endpoints, including percentage of patients with plasma HIV-1 RNA < 50 copies/ml, were consistent with those of the primary analysis. No patient developed treatment-emergent resistance to any of the medicines used in the study[1].

**Table 1. Virological outcomes at week 48**

| Outcome | Treatment difference | |
|---|---|---|
| **Study GS-US-380-1489: virological success** | | |
| Study medicine | Biktarvy® | Triumeq® |
| n | 314 | 315 |
| HIV-1 RNA < 50 copies/ml, n (%) | 290 (92.4) | 293 (93.0) |
| Difference in % (95% CI) | −0.6 (−4.8 to 3.6)* | |
| p value | 0.78 | |
| **Study GS-US-380-1490: virological success** | | |
| Study medicine | Biktarvy® | Dolutegravir + Descovy® |
| n | 320 | 325 |
| HIV-1 RNA < 50 copies/ml, n (%) | 286 (89) | 302 (93) |
| Difference in % (95% CI) | −3.5 (−7.9 to 1.0)* | |
| p value | 0.12 | |
| **Study GS-US-380-1844: proportion of patients with HIV-1 RNA ≥ 50 copies/ml** | | |
| Study medicine | Biktarvy® | Triumeq® |
| n | 282 | 281 |
| HIV-1 RNA ≥ 50 copies/ml, n (%) | 3 (1.1) | 1 (0.4) |
| Difference in % (95% CI) | 0.7 (−1.0 to 2.8)† | |
| p value | 0.62 | |

* Biktarvy® meet the pre-defined criterion for non-inferiority (a lower bound of a two-sided 95% CI of −12%)
† Biktarvy® meet the pre-defined criterion for non-inferiority (a lower bound of a two-sided 95% CI of −4%)
CI: confidence interval; HIV-1: human immunodeficiency virus-type 1; n: number of patients; RNA: ribonucleic acid.

The company submission also included a study to evaluate the switching to Biktarvy® compared with continuing a regimen of ritonavir- or cobicistat-boosted atazanavir or darunavir plus either Truvada® or Kivexa® in virologically suppressed patients (GS-US-

380-1878). The comparison of Biktarvy® to a protease inhibitor-based regimen provides additional data to support the place of such integrase inhibitors into the HIV therapeutic strategy[2].

### 3.3 Systematic review and NMA

To address the lack of direct comparative evidence, the company submitted a systematic literature review and NMA to estimate the efficacy and safety of Biktarvy® compared to existing treatments including Genvoya®[1]. The review included all phase III or IV studies that could contain data for the comparison of Biktarvy® with triple therapy regimens containing a Truvada®, Descovy® or Kivexa® backbone with a third agent (non-nucleoside reverse transcriptase inhibitor [NNRTI], integrase inhibitor, or protease inhibitor), and dual therapy regimens. Studies included patients with HIV-1 and who were either treatment-naïve or treatment-experienced and aged 18 years or older. The aim of the NMA was to capture all relevant data for triple therapy regimens and to inform the comparison with Genvoya® as well as reinforce the clinical trial data for Triumeq®. However, there are a number of limitations associated with the NMA[1].

A total of 4,988 records were found through database searching[1]. After de-duplication and sifting, 214 were found to fulfil the inclusion criteria, representing 36 unique clinical trials. There was considerable between-trial heterogeneity in terms of study design and prior regimens in the treatment-experienced patients; consequently, only the results of the NMA performed on treatment-naïve patients were presented by the applicant company. A total of 24 randomised controlled studies investigated NRTI-based ART regimens in the treatment-naïve population. Of these studies, 15 investigated integrase inhibitor regimens and 11 investigated protease inhibitor regimens[1].

Sensitivity analyses were performed to address the heterogeneity across studies. The sensitivity analyses supported the conclusions of the main analyses.

The results of the NMA presented by the company support non-inferiority in efficacy for Biktarvy® versus Triumeq® in treatment-naive patients. The NMA also suggests that there were no significant differences for Biktarvy® versus either Triumeq® and Genvoya® in terms of efficacy at week 48[1], however the NMA is subject to limitations (see section 3.6).

### 3.4 Comparative safety

The assessment of adverse reactions is based on safety data from across all phase II and phase III studies with Biktarvy®. A total of 1511 patients had received at least one dose of Biktarvy®, including 1206 patients from the randomised phases of the phase III studies[2]. The number of patients with a high duration of treatment (≥ 72 weeks) is very limited but the duration of exposure was similar between groups within each study[2]. Biktarvy® demonstrated a renal safety profile and bone safety profile comparable with that of Triumeq®, a regimen that is not associated with renal toxicity or bone toxicity[2].

Although no liver hypersensitivity reaction or severe drug-induced liver disease occurred in patients treated with Biktarvy®, higher rates of transaminases elevations and hyperbilirubinemia were observed compared to dolutegravir-based regimen[2]. The Committee for Medicinal Products for Human Use required an amendment to the study protocols GS-US-380-1489 and GS-US-380-1844 to include recommendations for the management of potential hepatobiliary toxicity. Hepatotoxicity will be actively monitored through periodic safety update reports[2].

The company report that a statistically significantly greater number of patients reported improvements from baseline in various symptoms such as fatigue/loss of energy,

dizziness/light headedness, nausea and vomiting and difficulty sleeping in the Biktarvy® group compared to Triumeq®[12].

The Committee for Medicinal Products for Human Use concluded that no new risks or safety issues have been identified for the fixed dose combination of Biktarvy®, and it is generally safe and well tolerated in people with HIV[2]. The adverse event profile was generally similar in ART-naïve and virologically suppressed adults, with similar rates of adverse events and severe adverse events related to the medicine, and adverse events leading to discontinuation of the treatment. The most frequently reported adverse reactions were headache (4.6%), diarrhoea (4.6%) and nausea (4.1%). Seven deaths were reported across the studies; four in patients receiving Biktarvy®. None of the deaths were considered related to Biktarvy®[2].

### 3.5 Ongoing studies

The two switch studies GS-US-380-1844 and GS-US-380-1878 are due to be published in Q2 2018. In addition, the patient reported outcome results from studies GS-US-380-1489 and GS-US-380-1844 are due to be published in Q2/Q3 2018.

Additional studies of Biktarvy® in women (GS-US-380-1961) and virologically suppressed adolescents and children (GS-US-380-1474) are ongoing and expected to report in 2018.

### 3.6 AWTTC critique

- The company submission included studies which support the non-inferiority of Biktarvy to the comparator Triumeq® in ART-naïve and/or virologically supressed people with HIV. There is, however, no direct comparative evidence for Biktarvy® versus Genvoya® and efficacy data for Biktarvy® versus Triumeq® is limited to 48-week analyses.
- To address the lack of direct comparative evidence, the company submitted a systematic literature review and NMA to estimate the efficacy and safety of Biktarvy® compared to existing treatments including Genvoya®. However, the NMA is subject to a number of limitations.
- Due to marked heterogeneity in study design and patient populations, the NMA does not include analysis focused on the virologically-suppressed, treatment-experienced population. Virological failure could also not be analysed as a result of heterogeneity. Many of the comparisons in the NMA are derived via one study only. This increases uncertainty. The NMA is also largely informed by data collected over just 48 weeks for the primary outcomes. In addition some studies are entirely populated with female participants. Biktarvy® is also not well-connected in any of the outcome networks; it is connected via Triumeq® only. Other limitations include the inclusion of studies which are not characterised by randomisation and some that are open-label. However, results from sensivity analyses were similar to base-case results, suggesting that inclusion of these studies has limited impact.
- The credible intervals of the NMA demonstrate uncertainty in the treatment comparisons, as the majority of credible intervals cross the null value and some are notably wide.
- Clinical expert opinion sought by AWTTC suggests that the choice of comparators was appropriate for this submission, however, there is uncertainty around whether the choice of comparators reflects a comprehensive representation of all treatment options available in Wales. The company's rationale for using these comparators was that they are triple therapies available as a single tablet regimen and that they both contain a NRTI backbone with an

integrase inhibitor as the third agent. However, it remains a limitation and source of uncertainty that there is no comparison with a wider range of comparators.

- Direct safety and clinical efficacy data is limited to 48-week analyses and the number of patients with a high duration of treatment (≥ 72 weeks) is limited; therefore, uncertainties on the long term safety of Biktarvy® must be considered.
- All tests and monitoring for Biktarvy® would be the same as currently used for HIV treatments. However the company suggest that there are patient reported differences in safety profiles between the medicines, which could impact on quality of life.
- Biktarvy® is the smallest integrase inhibitor-containing single treatment regimen and has no requirement to be taken with food[1].

## 4.0 COST-EFFECTIVENESS

### 4.1 Cost-effectiveness evidence

#### 4.1.1 Context

The company submission includes a cost-minimisation analysis (CMA) comparing Biktarvy®, an oral fixed dose combination comprising bictegravir 50 mg, emtricitabine 200 mg and tenofovir alafenamide 25 mg, with Triumeq® (combination of abacavir 600 mg, lamivudine 300 mg and dolutegravir 50 mg) and Genvoya® (combination of elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir alafenamide 10 mg), in adults infected with HIV-1 without any known mutations associated with resistance to the individual components of Biktarvy®. It is anticipated that Biktarvy® will be used as a first line treatment option, or as an alternative treatment option for treatment-experienced patients who require to switch from existing therapy due to unsatisfactory efficacy or tolerance, or for the purpose of regimen simplification.

A simple Excel-based cost-minimisation model is used to estimate the difference in costs between Biktarvy® versus Triumeq® and Genvoya®. The company assume equivalence (close comparability) across all relevant outcome domains. This assumption is based on clinical data collected via head-to-head non-inferiority trials for Biktarvy® versus Triumeq®, which included both the treatment-naïve and treatment-experienced populations. The company also conducted an NMA to reinforce the Biktarvy® versus Triumeq® comparison and to compare Biktarvy® versus Genvoya®. However, the NMA was conducted using studies focused on treatment-niave patients only; therefore it does not include comparisons in the virologically-supressed, treatment-experienced population. The model adopts an NHS/Personal Social Services perspective and a time horizon of one year; it is assumed that the same cost-impact will be seen year-on-year. No discounting is applied given the short time horizon of the model. The analyses consider only the medicine acquisition costs for each single-tablet regimen. Resource use costs are not included. There are Wales Patient Access Scheme (WPAS) discounts on each of the regimens. WPAS prices are used in the base case for Biktarvy® and Genvoya® but the list price is applied for Triumeq®, informed by the Monthly Index of Medical Specialities[13].

The sensitivity analyses conducted by the company explore the impact of price discounts for Triumeq® in increments from 5% to 95%. Scenario analyses further explore alternative comparators, the full set of British HIV Association (BHIVA) preferred ARTs, weighted to reflect market shares in Wales and based on the assumption of equivalence further to the NMA. The first scenario used the proprietary medicine list prices for all medicines except Kivexa®, where the generic pricing was used. The second scenario used generic pricing for Truvada®, Atripla® and Kivexa® regimens.

### 4.1.2 Results

The results of the base case analysis and sensitivity analyses are given in Table 2. Biktarvy® is less costly in the base case and in the majority of scenario and sensitivity analyses conducted.

**Table 2. Results of the base case analysis and scenario/sensitivity analyses**

| Scenario | Costs | Biktarvy® | Comparator | Difference | Plausibility |
|---|---|---|---|---|---|
| **Base case** | | | | | |
| Biktarvy® versus Triumeq® | Medicine acquisition costs | ¶¶* | £9,718† | ¶¶ | This is not reflective of current acquisition cost differences in Wales, due to the existence of a WPAS on Triumeq® |
| Biktarvy® versus Genvoya® | Medicine acquisition costs | ¶¶* | ¶¶* | ¶¶ | This cost comparison is reflective of current cost differences in Wales |
| **Scenario analysis (A)** | | | | | |
| Biktarvy® versus weighted comparison of full set of BHIVA-preferred ART regimens (proprietary list prices, except Kivexa® [which has generic pricing] with PAS on Stribild® and Genvoya®) | Medicine acquisition costs | ¶¶* | ¶¶* | ¶¶ | This potentially offers a more comprehensive approach to choice of comparators - but does not take into account PAS on Triumeq® |
| **Scenario analysis (B)** | | | | | |
| Biktarvy® versus weighted comparison of full set of BHIVA-preferred ART regimens (all Truvada® , Kivexa® and Atripla® regimens using generic prices and with PAS on Stribild® and Genvoya®) | Medicine acquisition costs | ¶¶* | ¶¶ | ¶¶ | This potentially offers a more comprehensive approach to choice of comparators - but does not take into account PAS on Triumeq® |

* WPAS price
† List price – WPAS available for this medicine
¶¶ Commercial in confidence figure removed
Differences may not compute due to rounding
ART: antiretroviral therapy; BHIVA: British HIV Association; PAS: Patient Access Scheme; WPAS: Wales Patient Access Scheme.

The results of the sensitivity analyses suggest that Biktarvy® is no longer cost saving versus Triumeq® when a WPAS discount [commercial in confidence figure removed] is applied to Triumeq®. Above this threshold, Biktarvy® is associated with an additional cost ranging from [commercial in confidence figure removed] when a discount of [commercial in confidence figure removed] is applied to the list price.

### 4.1.3 AWTTC critique

The reliability of the CMA is dependent on the extent to which Biktarvy® is considered to be therapeutically equivalent to the comparators. The company justify the use of a CMA, as opposed to a cost-utility analysis (CUA), on the basis that the supporting trials, GS-US-380-1489[10] and GS-US-380-1844[14], report non-inferiority for Biktarvy® versus Triumeq®, in treatment-naive patients and virologically supressed/treatment-experienced patients, respectively. A Bayesian NMA is reported to support non-inferiority in efficacy for Biktarvy® versus Triumeq® in treatment-naive patients. The NMA also suggests no significant differences for Biktarvy® versus Genvoya® in terms of efficacy. However, the NMA is subject to limitations (see section 3.6).

Strengths and limitations of the economic analysis include:

- In the absence of well-designed equivalence studies and evidence of close comparability of all other effects (including impact on health-related quality of life, adherence, administration issues, etc.), in addition to the limitations of the NMA and efficacy data (see Section 3.6), AWTTC consider CMA to be an inappropriate approach in this instance. The company acknowledge that there are reported differences in safety profiles between the medicines, which could impact on quality of life. Furthermore, Biktarvy® is the smallest integrase inhibitor-containing single treatment regimen and has no requirement to be taken with food, which have implications in terms of enhanced potential for compliance. These differences are likely to favour Biktarvy®; however, the impact of these cannot be quantified using CMA.
- Deviance Information Criterion (DIC) results have been used to choose between fixed and random effects models for the NMA (i.e. the model with the lowest DIC has been deemed the best predictor). However, given that the DIC differences between models are less than 5 for every outcome of interest, and that the studies included in the NMA are not homogenous, then random effects models would seem to be more appropriate in this instance.
- The comparators have been informed by Welsh clinical opinion. However, BHIVA guidelines include a wider range of regimens. Welsh data report that the comparators used in the model are prescribed in Wales; but there is also relatively high usage of alternative therapies[15]. It is uncertain whether the comparators used in the base case offer a comprehensive and complete representation of treatment options in Wales for the targeted patient populations (i.e. the model may not include all of the most appropriate comparators). Furthermore, it would likely have been more informative to model the two targeted populations in distinct models, to include appropriate comparators for each (as these possibly vary between the two groups).
- The time horizon used in the analysis is shorter than would be expected for a chronic condition.
- The costs included in the model are not comprehensive. They do not take into account monitoring, adverse events or other NHS resource use. The company proposes that these are equivalent; however, there is no evidence to support this for adverse events and other NHS resource use. Whilst it is acknowledged that the monitoring costs are likely to be equivalent, it is usually standard practice to report all relevant costs in a CMA.

### 4.2 Review of published evidence on cost-effectiveness

A literature search by AWTTC did not identify any studies relevant to the cost-effectiveness of Biktarvy® versus Triumeq® or Genvoya® in the treatment of adults infected with HIV-1 without any known mutations associated with resistance to the individual components of Biktarvy®.

## 5.0 BUDGET IMPACT

### 5.1 Budget impact evidence

#### 5.1.1 Context and methods

The company has estimated that there will be 1,835 patients with HIV-1 in Wales in Year 1. This estimate is based on Public Health England (PHE) prevalence figures for Wales (captured in 2016)[16]. To calculate the number of patients who require treatment in Wales, the company have combined prevalence estimates, with an annual mortality rate of 0.65% and an annual incidence of 157 patients per year. The assumed mortality rate and annual incidence reflect the average number of deaths and diagnoses reported by PHE in Wales between 2012 and 2016[16]. An assumed market share of 5.1% in Year 1, increasing to 13.8% in Year 5 is further applied to estimate the number of patients likely to be prescribed Biktarvy® in Wales for the indication covered in the submission. The company provide a breakdown of how comparator medicines Triumeq® and Genvoya®, which are assumed to have equal 50% market share, are likely to be displaced as a result. Sensitivity analyses have been performed to explore the impact of varying the projected base case market share and patient population size by ± 20%. Further analyses explore the impact of a WPAS when the acquisition cost of Triumeq® is discounted between 5–95%.

#### 5.1.2 Results

The budget impact is presented in Table 3. The company estimates that introduction of Biktarvy® would lead to an approximate overall saving of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of Triumeq® and Genvoya®.

The company-conducted sensitivity analyses varying the projected base case market share of Biktarvy® and patient population size by ± 20% resulted in cost savings between [commercial in confidence figure removed] in Year 1, and savings between [commercial in confidence figure removed] in Year 5. The scenario analyses exploring price discounts for Triumeq® reveal that Biktarvy® is likely to be cost-saving in all years until the discount reaches [commercial in confidence figure removed] - at which point there becomes a positive budget impact (i.e. Biktarvy® is associated with additional costs).

**Table 3. Company-reported costs associated with use of Biktarvy® for the treatment of HIV-1 infection**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Number of eligible patients** | 1,835 | 1,992 | 2,149 | 2,305 | 2,462 |
| **Uptake of new medicine (%)** | 5.1% | 9.8% | 11.8% | 12.8% | 13.8% |
| **Number of patients receiving new medicine allowing for discontinuations** | 93 | 194 | 252 | 293 | 338 |
| **Medicine acquisition costs in a market without new medicine** | ¶¶ | ¶¶ | ¶¶ | ¶¶ | ¶¶ |
| **Medicine acquisition costs in a market with new medicine** | ¶¶ | ¶¶ | ¶¶ | ¶¶ | ¶¶ |
| **Net medicine acquisition costs** | ¶¶ | ¶¶ | ¶¶ | ¶¶ | ¶¶ |
| **Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable** | ¶¶ | ¶¶ | ¶¶ | ¶¶ | ¶¶ |
| ¶¶ Commercial in confidence figure removed | | | | | |

### 5.1.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact.
- The budget impact considerations are limited to acquisition costs only; other resource use is not included (e.g. monitoring costs and costs associated with adverse events). However, monitoring costs are expected to be comparable for the medicines included in the analyses.
- The medicines used to calculate the effects of market share displacement in the base case are limited to the two comparators used for the CMA. These projections are therefore, possibly limited in scope. Further sensitivity analyses would have been beneficial to explore the impact of displacing other possible comparators.
- The incidence and mortality estimates have been informed via an averaging approach, rather than trend analysis. This approach to analysis does not factor in the potential effects of recently improved access to preventative treatments in Wales.

## 5.2 Comparative unit costs

Acquisition costs for treatments for HIV-1 infection are given in Table 4.

### Table 4. Examples of medicine acquisition costs

| Regimens | Unit cost / Pack price | Example doses | Approximate costs per patient (per annum) |
|---|---|---|---|
| **Integrase inhibitors / NRTIs** | | | |
| Biktarvy® | ¶¶ | 1 tablet once daily | ¶¶ |
| Triumeq® | ¶¶ | 1 tablet once daily | ¶¶ |
| Genvoya® | ¶¶ | 1 tablet once daily | ¶¶ |
| Stribild® | ¶¶ | 1 tablet once daily | ¶¶ |
| **NRTIs** | | | |
| Atripla® | £533 | 1 tablet once daily | £6,489 |
| Eviplera® | £526 | 1 tablet once daily | £6,404 |
| Odefsey® | £526 | 1 tablet once daily | £6,404 |
| **Other regimens, including generics** | | | |
| Truvada® plus Tivicay® | £356 + ¶¶ | 2 tablets once daily | (£4,331 + ¶¶)<br>¶¶ |
| Emtricitabine with tenofovir disproxil plus dolutegravir | £107* + ¶¶ | 2 tablets once daily (without resistance) | (£1,303 + ¶¶)<br>¶¶ |
| Emtricitabine with tenofovir disproxil plus efavirenz | £107* + £30 * | 2 tablets once daily | (£1,303 + £365)<br>£1,668 |
| Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[5,17-24].<br>Costs are predominantly based on the Monthly Index of Medical Specialities list prices as of 23/07/2018[13].<br>¶¶ Commercial in confidence figure removed<br>* Based on British National Formulary list prices as of 23/07/2018[25].<br>This table does not imply therapeutic equivalence of drugs or the stated doses.<br>NRTI: nucleoside reverse transcriptase inhibitors | | | |

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