Common Drug Review

Fixed-Dose Combination Review Report

July 2015

Drug	dolutegravir sodium, abacavir sulfate and lamivudine (Triumeq)
Indication	For treatment of human immunodeficiency virus (HIV-1) infection in adults
Listing request	As per indication
Manufacturer	ViiV Healthcare ULC

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ART	antiretroviral therapy
AUC	area under the curve
CI	confidence interval
COBI	cobicistat
C_{max}	maximum observed concentration
CTAC	Canadian Treatment Action Council
CYP	cytochrome P450
DHHS	United States Department of Health and Human Services
DTG	dolutegravir
EFV	efavirenz
EMEA	European Medicines Agency
EVG	elvitegravir
FDC	fixed-dose combination
FTC	emtricitabine
IAS	International Antiviral Society
INSTI	integrase stand transfer inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
RPV	rilpivirine
STR	single-tablet regimen
TDF	tenofovir

EXECUTIVE SUMMARY

Triumeq is a single-tablet regimen (STR) for the treatment of HIV infection that contains dolutegravir (DTG), abacavir (ABC), and lamivudine (3TC). One tablet formulation is available containing 50 mg DTG, 600 mg ABC, and 300 mg 3TC, and the dose is one tablet daily (DTG/ABC/3TC STR).[1] The objective of this review was to evaluate the manufacturer-submitted evidence on the bioequivalence, safety, and costs of DTG/ABC/3TC STR for the treatment of HIV-1 infection in adults.

Indication under review
Triumeq is indicated for the treatment of the HIV-1 infection in adults
Listing criteria requested by sponsor
As per indication

The manufacturer's rationale suggests DTG/ABC/3TC STR offers a unique combination of advantages over other regimens for HIV, including a broad indication for HIV-infected patients; no restrictions based on baseline viral load or treatment experience; increased compliance due to the STR; lack of significant cytochrome P450 (CYP) 3A enzyme interactions; and the ability to dose without regard for food. The manufacturer's assertions regarding the current treatment paradigm for HIV infection, the place of STRs within it, and the potential benefits and place in therapy for DTG/ABC/3TC STR are generally accurate. The components of DTG/ABC/3TC STR are currently recommended as initial treatment for HIV infection in the most recent edition of the United States Department of Health and Human Services (DHHS) Guidelines. Treatment guidelines such as those from the DHHS also support the assertion that switching from a multiple-tablet regimen to a fixed-dose combination (FDC) pill is likely to improve convenience and maintain adherence. While benefits to adherence are expected with the use of STRs, the magnitude and statistical and clinical significance of these benefits were inconsistent, based on a review of the studies provided by the manufacturer to support this argument. Two of three studies cited by the manufacturer suggest a statistically significant increase in adherence ranging from 2% to 18%. One study suggested there was no difference in adherence based on STR compared with keeping patients on their baseline (multi-pill) regimens.

A single phase 3 randomized study, SINGLE, has compared DTG/ABC/3TC (administered as DTG + ABC/3TC FDC) with another STR, Atripla (emtricitabine [FTC]/tenofovir [TDF]/efavirenz [EFV]), in treatment-naive patients. Overall, the DTG regimen was more tolerable than EFV/TDF/FTC, which led to statistically superior virologic response at the week 48 primary end point (i.e., proportion of subjects with HIV-1 ribonucleic acid [RNA] less than 50 copies per millilitre [c/mL]); 88% of patients in the DTG group achieved this outcome compared with 81% in the FTC group. A superior virologic response was maintained through 96 weeks of therapy. Other trials of DTG, including the trials in treatment-experienced patients, involved more than one backbone therapy (i.e., not just ABC/3TC); hence, the results are less generalizable to the DTG/ABC/3TC STR.

A single pivotal study assessed the bioequivalence of DTG/ABC/3TC STR with DTG and ABC/3TC FDC administered separately. In study ING114580, DTG/ABC/3TC (50 mg/600 mg/300 mg) STR demonstrated bioequivalence in healthy adults to DTG (50 mg) + ABC/3TC (600 mg/300 mg); 90% confidence intervals (CIs) for the geometric least squares (GLS) mean ratios for area under the curve (AUC) and maximum observed concentration (C_{max}) were within the range of 0.8 to 1.25; this is in line with Health Canada's recommended criteria.

Given the established bioequivalence of DTG/ABC/3TC STR with DTG and ABC/3TC administered separately, the safety results from the SINGLE trial are applicable to DTG/ABC/3TC STR. The data from SINGLE trial suggest there were lower proportions of drug-related adverse events and withdrawal due to adverse events for patients treated with DTG+ABC/3TC compared with EFV/TDF/FTC. The manufacturer also provided safety data from the bioequivalence study (ING 114580), but these are of limited utility in assessing the harms of DTG/ABC/3TC STR, as this was a single-dose study.

At the submitted price, DTG/ABC/3TC STR ($41.01 daily) is less expensive than the individual components of DTG ($18.50) and ABC/3TC ($23.62), resulting in a cost-saving of $1 daily. DTG/ABC/3TC STR is less expensive than other DHHS-recommended first-line STRs, including EFV/TDF/FTC, FTC/RPV/TDF, and cobicistat (COBI)/EVG/FTC/TDF (cost savings ranging from $1 to $5 daily).

1. INTRODUCTION

Triumeq is a single-tablet regimen (STR) for the treatment of HIV infection that contains dolutegravir (DTG), abacavir (ABC), and lamivudine (3TC). One tablet formulation is available containing DTG 50 mg, ABC 600 mg, and 3TC 300 mg (DTG/ABC/3TC STR).[1] DTG is an orally active HIV integrase strand transfer inhibitor (INSTI) for the treatment of HIV infection in combination with other antiretroviral drugs.[2] ABC is a nucleoside reverse transcriptase inhibitor (NRTI), and is a potent, selective inhibitor of HIV-1 and HIV-2, including HIV-1 isolates with reduced susceptibility to zidovudine, 3TC, zalcitabine, didanosine, and nevirapine.[3] 3TC is an NRTI and is a potent, selective inhibitor of HIV-1 and HIV-2. The principal mode of action of 3TC is inhibition of HIV reverse transcription via viral DNA chain termination.[4]

DTG/ABC/3TC STR is indicated for the treatment of HIV-1 in adults. DTG/ABC/3TC STR can be taken with or without food.[5] The recommended dose is one tablet once daily.[5]

Indication under review
For the treatment of the HIV-1 infection in adults
Listing criteria requested by sponsor
As per indication

2. RATIONALE AND PLACE IN THERAPY

2.1 Manufacturer-Submitted Information on Rationale (Verbatim)

Triumeq (DTG/ABC/3TC) is a new STR that combines the clinical benefits of the recently approved INSTI Tivicay (DTG)[1] as the third drug ("anchor") with a well-established NRTI backbone regimen of Kivexa (ABC/3TC)_ENREF_1.[2] Although antiretroviral regimens are selected on the basis of their components, STRs have established themselves as the standard of care for the treatment of HIV infection in Canada and globally over the past few years. In addition to providing the general benefits common to all STRs, including low bill burden to facilitate adherence, Triumeq offers distinct advantages over currently available STRs due to its anchor drug, DTG. Triumeq has a broad indication for treatment of HIV-infected patients, without limitations related to baseline viral load or treatment experience (except in cases of resistance to any of the components).

Tivicay (DTG) was given a list recommendation by the CADTH Common Drug Review (CDR) on August 18, 2014, while Kivexa (ABC/3TC) was given a list recommendation on December 6, 2005, and has an open listing across Canada.[3] _ENREF_3

Although combination antiretroviral therapy (ART) with HIV protease inhibitors (PIs) and reverse transcriptase inhibitors has demonstrated significant improvement in AIDS-related morbidity and mortality, a number of issues remain to be addressed that could lead to improvements in the existing armamentarium of HIV therapy. Ideal characteristics for new treatment regimens in comparison with currently available therapies include activity against drug-resistant HIV, less toxicity and greater tolerability, durability and higher barriers to developing resistance, fewer drug interactions, and a convenient dosing schedule. Triumeq provides such improvements over existing regimens.

There is substantial evidence in the literature that supports the benefit of streamlined treatment regimens, including those with once-daily administration and a minimized pill burden. In addition, clinical data support patient acceptance of and preference for STRs, as well as improved compliance with STRs.[4-8] In a study to evaluate therapy simplification, DeJesus et al.[9] found that when subjects were switched in a 2:1 ratio to the STR Atripla (efavirenz [EFV]/tenofovir [TDF]/emtricitabine [FTC]) instead of staying on their baseline regimen (a three- to four-drug, multi-pill, once-daily regimen), the STR regimen led to improvement in self-reported outcomes, including perceived ease of taking the regimen and overall preference for the STR. Airoldi and colleagues[10] had similar findings when switching from a dual NRTI plus EFV regimen to Atripla. In this study, the adherence rate at one month was improved modestly, but statistically significantly ($P < 0.01$), and this continued through six months of follow-up. Their results also indicated a better perceived quality of life and higher patient preference for the STR. A study by Bangsberg et al.[11] evaluated the use of Atripla and showed that it was a key factor in improving treatment compliance and viral suppression in a high-risk, marginalized population of homeless or near-homeless HIV-infected people. These data support the benefit of an STR treatment for populations where compliance may be more challenging.

As HIV infection is an incurable, lifelong condition, the availability of durable treatment options is critical to the successful treatment of patients. Patient compliance features prominently in the long-term success of any antiretroviral regimen because poor compliance due to factors such as pill burden has been linked to the increased development of HIV drug resistance, which in turn inevitably leads to the inability of a regimen to suppress the virus. The use of STRs in the treatment of HIV may decrease the potential for development of selective resistance to any of the individual components as patients must take either an entire regimen via a single pill or none of the regimen; they cannot selectively take only one or two drugs of their multi-drug regimen. This is important given that monotherapy (or "virtual monotherapy" due to partial compliance with a regimen) is a risk for early development of viral resistance to that drug, eventual treatment failure, and the elimination of future treatment options due to within-class cross-resistance to other drugs.

Currently, the STRs recommended by treatment guidelines[12] are non-nucleoside reverse transcriptase inhibitor (NNRTI)-based, Atripla, and Complera [FTC/rilpivirine (RPV)/TDF STR), are recommended only in patients with baseline HIV viral load of < 100,000 copies/mL [c/mL]), and Stribild, the first INSTI-based STR containing the INSTI elvitegravir (EVG), along with the pharmacokinetic (PK) booster cobicistat (COBI) and the NRTIs TDF and FTC. However, despite the availability of these STRs, there is still a need for Triumeq. All of the current STR options, with the exception of Trizivir (ABC/3TC and the NRTI zidovudine), contain TDF, which may not be a suitable treatment option for some patients, such as those with renal insufficiency or osteopenia (or at risk for these conditions), or those with resistance or intolerance to TDF.[13,14,15]

Other potential treatment advantages for Triumeq versus most other available STRs include a lack of significant cytochrome P450 (CYP) 3A enzyme interactions, and the ability to dose without regard to food. NNRTIs are substrates of CYP3A enzymes, and the STR Stribild includes the CYP3A4 inhibitor COBI in its formulation to provide PK boosting for its INSTI component, EVG. All components of Triumeq have few drug interactions, which would allow for its co-administration with drugs commonly used to treat comorbid conditions.

The Health Canada filing for Triumeq was based on the demonstration of bioequivalence of Triumeq with a regimen composed of its components DTG and ABC/3TC FDC (Study ING114580). [26,27] The efficacy, safety, and tolerability of Triumeq were established through a program of clinical trials

supporting the third drug DTG, including one pivotal study (SINGLE) and several supportive studies (SPRING-2, FLAMINGO, SAILING).

The randomized clinical trial SINGLE has shown that the DTG + ABC/3TC FDC regimen was more tolerable overall than Atripla, which led to statistically superior virologic response versus Atripla at the week 48 primary end point (i.e., proportion of subjects with HIV-1 ribonucleic acid [RNA] < 50 c/mL), and continued to demonstrate a superior virologic response through 96 weeks of therapy.[16,17] The DTG + ABC/3TC FDC regimen has been used in other ART-naive studies as well: SPRING-2 (DTG non-inferior to raltegravir [RAL] twice daily with ABC/3TC or TDF/FTC at week 48 and 96 weeks)[18,19] and FLAMINGO (DTG statistically superior to darunavir/ritonavir, both with ABC/3TC or TDF/FTC at 48 weeks).[20,21] Importantly, none of the ART-naive subjects treated with this regimen have developed resistance to any of the components of the regimen. This is not the case for the comparator groups in the DTG program (for which both NRTI and third-drug resistance has been observed), and stands in contrast to the frequency of treatment-emergent resistance that has been observed with NNRTI- and other INSTI-based STRs that are currently marketed.[22,23,24] In the SAILING study, DTG-based therapy demonstrated superiority to RAL-based therapy in INSTI-naive, treatment-experienced patients. Significantly fewer subjects experienced treatment-emergent INSTI resistance on DTG once daily versus RAL twice daily (DTG, 4/354 [1%]; RAL, 17/361 [5%]; $P = 0.003$).[25]

Therefore, Triumeq will be a valuable new therapeutic option for patients and prescribers, as it allows for the benefits of a maximally simplified daily treatment (i.e., a once-daily STR). Finally, Triumeq may represent the best choice for patients with HIV infection who would be optimally treated with a DTG-based regimen, either due to tolerance concerns or resistance concerns (e.g., those with virus resistant to NNRTIs or PIs), and who would benefit from the adherence advantages associated with STRs.

2.2 Manufacturer-Submitted Information on Place in Therapy (Verbatim)

The components of Triumeq are currently recommended for initial treatment in the US Department of Health and Human Services (DHHS) treatment guidelines.[12] There are no recent national HIV treatment guidelines in Canada. In general, physicians treating Canadian HIV patients primarily refer to the US DHHS guidelines or their respective provincial guidelines (British Columbia and Quebec only). The most updated versions of the provincial guidelines were not available, so only the DHHS guidelines are discussed.

Triumeq is anticipated to be used in HIV-infected patients initiating treatment, as it provides two NRTIs, including ABC/3TC and the INSTI DTG in a single tablet. Triumeq is expected to be used as a replacement to DTG+ABC/3TC FDC taken concomitantly.

The doses of each component of Triumeq are consistent with the doses currently available and no inappropriate dosing of either component is anticipated with the introduction of Triumeq. The separate components of DTG, ABC, or 3TC should be considered in cases where dose adjustment or discontinuation of an individual component is indicated. Triumeq is not recommended for patients requiring dosage adjustments, such as patients with renal impairment (creatinine clearance [CrCl] < 50 mL/min). If a dosage reduction of ABC, a component of Triumeq, is required in patients with mild hepatic impairment, then the separate preparations of DTG, ABC, and 3TC should be used. Although HIV-specific numbers are not available, the prevalence of stage 3 and higher chronic kidney disease (estimated glomerular filtration rate [eGFR] < 60 mL/min) in the Canadian general population has been found to be 3.1% (using the chronic kidney disease epidemiology collaboration [CKD-EPI] equation). Despite the fact that these numbers might differ for the HIV population, the need for the use of

individual components for this reason is estimated to be marginal.[30] There are no titration issues, as monitoring of plasma drug levels is not necessary in regular clinical practice or when a switch to the individual components is needed due to a dose adjustment.

STRs are the standard of care in HIV treatment and availability of DTG in an STR will allow more patients to benefit from its favourable clinical attributes in a maximally simplified daily treatment (i.e., a once-daily STR) to facilitate adherence.

2.3 CDR Reviewer Comments

The manufacturer's assertions regarding the current treatment paradigm for HIV infection, the place of STRs within it, and the potential benefits and place in therapy of Triumeq (DTG/ABC/3TC STR) are generally accurate. Treatment guidelines such as those from the US DHHS support the assertion that switching from a multiple-tablet regimen to an FDC pill is likely to improve convenience and maintain adherence.[6,7] The components of DTG/ABC/3TC STR are currently recommended as initial treatment for HIV infection in the most recent edition of the DHHS Guidelines.[6] In addition, the most recent version of the International Antiviral Society (IAS)-USA Panel guidelines recommend DTG+ABC/3TC.[7]

A single phase 3 randomized study, SINGLE, has compared DTG/ABC/3TC (administered as DTG + ABC/3TC FDC) with Atripla (EFV/TDF/FTC STR) in treatment-naive patients. Overall, the DTG regimen was more tolerable than EFV/TDF/FTC STR, which led to statistically superior virologic response at the week 48 primary end point (i.e., proportion of subjects with HIV-1 RNA < 50 c/mL); 88% of patients in the DTG group achieved this outcome compared with 81% in the FTC group.[8] A superior virologic response was maintained through 96 weeks of therapy. Other trials of DTG, including the trials in treatment-experienced patients, involved more than one backbone therapy (i.e., not just ABC/3TC); hence, the results are less generalizable to the DTG/ABC/3TC STR.

Recommendations for treatment-experienced patients are more complex than those for treatment-naive patients. The DHHS recommends that a new regimen for such patients should include at least two, preferably three, fully active drugs. A fully active drug is defined as one that is expected to have antiretroviral activity on the basis of the patient's treatment history and drug-resistance testing results and/or the drug's novel mechanism of action.[7] The IAS-USA Panel recommends that for patients who have failed initial ART therapy, a second-line regimen should include a boosted PI due to the high barrier of resistance, especially when there is evidence of a compromised NRTI backbone. A boosted PI should be used with at least one fully active drug (NRTI, INSTI, or NNRTI).[6] In this context, there may be a scenario in which DTG/ABC/3TC STR could be an option for treatment-experienced patients if at least two components of the STR are still fully active drugs based on resistance testing. Since DTG/ABC/3TC STR contains ABC, it is recommended that patients are screened for the HLA-B*5701 allele. HLA-B*5701 allele-positive patients are at greater risk of developing a hypersensitivity reaction. As a result, patients with HLA-B*5701 should be excluded from treatment with DTG/ABC/3TC STR.[5]

DTG/ABC/3TC STR includes the recommended doses of ABC (600 mg) and 3TC (300 mg) (for adults weighing at least 30 kg).[3,4,9] However, the availability of DTG/ABC/3TC STR will not afford all patients treated with DTG/ABC/3TC the benefits of an STR. 3TC requires dosage adjustment for patients with impaired renal function (CrCl ≤ 50 mL/min), and is available as an individual component in a 150 mg strength. The lack of an STR including this dose of 3TC limits the ability of patients with impaired renal function to use DTG/ABC/3TC STR.[4] As well, DTG is only available as a 50 mg tablet administered once daily for adults weighing at least 40 kg who are treatment-naive and treatment-experienced patients who have INSTI resistance.[2] For treatment-experienced, INSTI-resistant patients, the recommended

dose of DTG is 50 mg twice daily. Therefore, an additional tablet of DTG would be required to achieve the necessary dose in patients with INSTI resistance. It is difficult to estimate what proportion of patients treated with DTG/ABC/3TC would require dosage adjustments of one component or another, but it is likely to be a relatively small minority.

While STRs are undoubtedly preferable to multi-pill regimens of the same components, the benefits of STRs on adherence may be overstated in the manufacturer's rationale. DeJesus et al. (2009) report self-reported adherence of 96% at baseline and at four, 12, 24, 36, and 48 weeks regardless of whether patients switched to EFV/TDF/FTC STR or stayed on their baseline regimens (SBRs).[10] These findings suggest little benefit in switching from SBRs to the STR.[10] Airoldi et al. (2010) found that one month following a switch from EFV + TDF + FTC or 3TC to EFV/TDF/FTC STR, there was a statistically significant increase in adherence rates from 93.8% to 96.1% ($P < 0.01$). The effect was maintained at six months with an adherence rate of 96.2%. Although this increase was statistically significant, the clinical importance of an increase in adherence of this magnitude is uncertain.[11] Bangsberg et al. (2010)[12] assessed adherence in a prospective cohort of homeless patients to EFV/TDF/FTC STR compared with multi-pill once daily therapy (ritonavir-boosted protease inhibitors [r-PI] and NNRTI regimens). EFV/TDF/FTC STR mean adherence was 86%, statistically significantly higher-than-mean adherence to all multi-pill daily regimens (73%), all r-PI regimens (75%), and all NNRTI regimens (68%).

The manufacturer's claim of an advantage for DTG/ABC/3TC STR with regard to CYP3A enzyme interactions is supported by the product monograph, as DTG did not inhibit these enzymes in vitro.[5] The importance to patients of the proposed advantage that DTG/ABC/3TC STR can be administered without consideration for food is unclear. In contrast, the other STRs are all recommended for administration with (FTC/RPV/TDF STR and Stribild) or without (EFV/TDF/FTC STR) food.[13-15]

3. BIOEQUIVALENCE

3.1 Manufacturer-Submitted Information on Bioequivalence (Verbatim)

The pivotal bioequivalence study ING114580 was a single-centre, randomized, two-part, open-label, crossover study in healthy adult subjects to evaluate the bioequivalence of a single combined formulated tablet of DTG 50 mg, ABC 600 mg and 3TC 300 mg compared with co-administration of the separate tablet formulations of DTG 50 mg and Epzicom (ABC/3TC FDC) in the fasted state, and to evaluate the effect of food on the bioavailability of the combined formulation.[26,27] The ABC/3TC FDC tablet used in this study is identical to the Kivexa tablet marketed in Canada. The study consisted of screening, treatment, and follow-up phases. The treatment phase was divided into two periods (Part A and Part B). Part A consisted of two single-dose treatment sequences (AB, BA) with a ≥ 7 day washout between doses. In Part A, 62 subjects received both treatment A and treatment B. Twelve subjects who completed Part A participated in Part B and received a single dose of the combined formulated tablet administered with a high-fat meal (Treatment C). There was a ≥ 7 day washout between doses in Part A and Part B. The follow-up phase was scheduled approximately seven to 14 days after the last dose of study drug.

- Treatment A: DTG 50mg/ABC 600mg/3TC 300mg FDC tablet, fasted
- Treatment B: DTG 50mg tablet plus a single Epzicom tablet, fasted
- Treatment C: DTG 50mg/ABC 600mg/3TC 300mg FDC tablet with a high-fat meal.

The FDC tablet formulation of DTG 50 mg, ABC 600 mg, and 3TC 300 mg met the criteria for bioequivalence with the separate tablet formulations of DTG 50 mg + ABC 600 mg/3TC 300 mg FDC. A summary is shown in Table 1. For each of DTG, ABC, and 3TC, the 90% CIs for the geometric least squares (GLS) mean ratios for each of the bioequivalence parameters were within the bioequivalence criteria range of 0.8 to 1.25.

The individual components of Triumeq, ABC, 3TC, and DTG have an uncomplicated pharmacokinetic profile and do not present high variability: all intra-subject per cent coefficients of variation for AUC (0-t) and C_{max} found in ING114580 were well below 30%.

TABLE 1: BIOEQUIVALENCE PROFILE FOR COMBINATION PRODUCTS

Parameter	ABC as DTG/ABC/3TC STR	ABC as DTG + ABC/3TC (ref)	3TC as DTG/ABC/3TC STR	3TC as DTG + ABC/3TC (ref)	DTG as DTG/ABC/3TC STR	DTG as DTG + ABC/3TC (ref)
AUC (0-t) ($mcg.h.ml^{-1}$)						
• Mean	14.31	14.86	12.70	13.09	42.74	45.40
• SD	3.525	3.369	3.238	2.772	13.149	13.641
• CV	25%	23%	26%	21%	31%	30%
• Ratio of means	0.960	ref	0.960	ref	0.943	ref
• 90% CI	0.939 to 0.980	ref	0.928 to 0.994	ref	0.888 to 1.001	ref
C_{max} ($mcg.ml^{-1}$)						
• Mean	4.13	4.52	2.20	2.35	2.53	2.64
• SD	0.948	1.146	0.640	0.588	0.696	0.741
• CV	23%	25%	29%	25%	28%	28%
• Ratio of means	0.920	ref	0.926	ref	0.961	ref
• 90% CI	0.867 to 0.977	ref	0.885 to 0.968	ref	0.906 to 1.019	ref
T_{max} (hr)						
• Mean	1.73	1.56	2.74	2.31	3.32	3.15
• SD	0.858	0.802	0.886	0.759	1.340	1.665
• CV	49%	51%	32%	33%	40%	53%

3TC = lamivudine; ABC = abacavir; CI = confidence interval; C_{max} = maximum observed concentration; CV = coefficient of variation; DTG = dolutegravir; ref = reference category; SD = standard deviation; STR = single-tablet regimen; T_{max} = time after administration of a drug when the maximum plasma concentration is reached.
Source: ING114580 Clinical Study Report Table 4.1, Table 4.2, Table 4.3, Table 4.4, Table 4.5, Table 4.6.

A copy of the Health Canada Reviewers' Report (also called Pharmaceutical Safety and Efficacy Assessment of the Comprehensive Summary — Bioequivalence) was not available at the time of this submission. It will be provided upon availability from Health Canada.

3.2 CDR Reviewer Comments

The manufacturer has provided an overview of the pivotal bioequivalence study (ING114580) to support the use of DTG/ABC/3TC STR in place of DTG and ABC/3TC for adult patients with HIV-1 infection. In study ING114580, DTG/ABC/3TC (50 mg/600 mg/300 mg) STR demonstrated bioequivalence to DTG (50 mg) + ABC/3TC (600 mg/300 mg); 90% CIs for the GLS mean ratios for AUC and C_{max} were within the range of 0.8 to 1.25. These criteria are in line with Health Canada's recommended criteria for bioequivalence of 80.0% to 125.0%.[16] Health Canada reviewers granted the approved indication based primarily on establishment of bioequivalence of DTG/ABC/3TC STR with the existing approved products DTG+ABC/3TC.[17]

4. HARMS

4.1 Manufacturer-Submitted Information on Harms (Verbatim)

The SINGLE trial compared DTG+ABC/3TC with Atripla (EFV/TDF/FTC STR) in treatment-naive patients and results are available for the 48- and 96-week analysis:[28,29]

- The proportion of patients with at least one adverse event was 89% with DTG+ABC/3TC and 92% with EFV/TDF/FTC STR at week 48; and 91% with DTG+ABC/3TC and 94% with EFV/TDF/FTC STR at week 96.
- The proportion of patients who reported at least one serious adverse event was 9% with DTG+ABC/3TC and 8% with EFV/TDF/FTC STR at week 48; and 11% with DTG+ABC/3TC and 12% with EFV/TDF/FTC STR at week 96.
- The proportion of patients who withdrew as a result of adverse events was 2% with DTG+ABC/3TC and 10% with EFV/TDF/FTC STR at week 48; and 3% with DTG+ABC/3TC and 12% with EFV/TDF/FTC STR at week 96.

Tables 2 and 3 provide details on drug-related adverse events in the SINGLE and ING114580 (bioequivalence) studies:

TABLE 2: TREATMENT-EMERGENT ADVERSE DRUG REACTIONS WITH ≥ 2% FREQUENCY IN SINGLE (ING114467)

Body System/Preferred Term	SINGLE 48-Week Analysis		SINGLE 96-Week Analysis	
	DTG+ABC/3TC (N = 414)	EFV/TDF/FTC STR (N = 419)	DTG+ABC/3TC (N = 414)	EFV/TDF/FTC STR (N = 419)
Psychiatric				
Insomnia	41 (10%)	23 (5%)	41 (10%)	25 (6%)
Nightmare	8 (2%)	14 (3%)	8 (2%)	14 (3%)
Depression	10 (2%)	9 (2%)	12 (3%)	14 (3%)
Abnormal dreams	26 (6%)	54 (15%)	27 (7%)	66 (16%)
Anxiety	4 (< 1%)	11 (3%)	4 (< 1%)	11 (3%)
Sleep disorder	6 (1%)	9 (2%)	6 (1%)	10 (2%)
Nervous System				
Dizziness	28 (7%)	133 (32%)	29 (7%)	139 (33%)
Headache	22 (5%)	31 (7%)	24 (6%)	31 (7%)
Somnolence	7 (2%)	19 (5%)	7 (2%)	18 (4%)
Gastrointestinal				
Nausea	42 (10%)	49 (12%)	44 (11%)	49 (12%)
Diarrhea	23 (6%)	36 (9%)	23 (6%)	35 (8%)
Vomiting	9 (2%)	10 (2%)	9 (2%)	11 (3%)

Body System/Preferred Term	SINGLE 48-Week Analysis		SINGLE 96-Week Analysis	
	DTG+ABC/3TC (N = 414)	EFV/TDF/FTC STR (N = 419)	DTG+ABC/3TC (N = 414)	EFV/TDF/FTC STR (N = 419)
Flatulence	10 (2%)	7 (2%)	10 (2%)	7 (2%)
Abdominal distension	7 (2%)	6 (1%)	7 (2%)	7 (2%)
Abdominal pain upper	6 (1%)	7 (2%)	6 (1%)	7 (2%)
Gastroesophageal reflux disease	8 (2%)	0	8 (2%)	0
General Disorders				
Fatigue	26 (6%)	26 (6%)	29 (7%)	28 (7%)
Asthenia	8 (2%)	5 (1%)	8 (2%)	5 (1%)
Skin and Subcutaneous Tissue				
Rash	4 (< 1%)	34 (8%)	4 (< 1%)	34 (8%)
Rash generalized	0	7 (2%)	0	7 (2%)
Pruritus	8 (2%)	6 (1%)	8 (2%)	6 (1%)
Ear and Labyrinth				
Vertigo	1 (< 1%)	16 (4%)	1 (< 1%)	16 (4%)
Metabolism and Nutrition				
Decreased appetite	4 (1%)	9 (2%)	4 (< 1%)	9 (2%)

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; TDF = tenofovir; STR = single-table regimen.
Source: ING114467 Clinical Study Report (CSR) 48 Weeks, Table 8.7; ING114467 CSR 96 Weeks, Table 8.7.

TABLE 3: TREATMENT-EMERGENT ADVERSE DRUG REACTIONS WITH ≥ 2% FREQUENCY IN ING114580 (BIOEQUIVALENCE)

Body System/Preferred Term	ING114580 – Bioequivalence	
	DTG/ABC/3TC STR (N = 65)	DTG+ABC/3TC (N = 65)
Nervous System		
Dizziness	1 (2%)	0
Headache	2 (3%)	4 (6%)
Gastrointestinal		
Nausea	10 (15%)	18 (28%)
Abdominal pain	0	1 (2%)
Vomiting	1 (2%)	0
General Disorders Feeling hot	0	1 (2%)

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; STR = single-table regimen.
Source: ING114580 Clinical Study Report, Table 2.4.

4.2 CDR Reviewer Comments

SINGLE is the only phase 3 trial of DTG and ABC/3TC (all other trials of DTG allowed for various backbones, not just ABC/3TC) compared with an EFV/TDF/FTC STR. Overall, drug-related adverse events (investigator-assessed) were reported more frequently for participants who received EFV/TDF/FTC STR compared with those who received DTG and ABC/3TC (66% versus 43%) in the SINGLE trial.[18] At both 48 and 96 weeks, insomnia occurred more frequently for patients treated with DTG and ABC/3TC compared with EFV/TDF/FTC STR. The frequency of abnormal dreams, headache, and insomnia were lower for patients treated with DTG and ABC/3TC compared with EFV/TDF/FTC STR. In addition, the proportion of

patients discontinuing due to adverse events at 48 and 96 weeks was lower for patients treated with DTG+ABC/3TC (2% and 3%, respectively) compared with EFV/TDF/FTC STR (10% and 12%).[18]

Given the established bioequivalence of DTG/ABC/3TC STR with DTG and ABC/3TC administered separately, the safety results from the SINGLE trial are applicable to DTG/ABC/3TC STR. The safety data from the bioequivalence study (ING 114580) are of limited utility in assessing the harms of DTG/ABC/3TC STR, as this was a single-dose study.

5. COST INFORMATION

5.1 Manufacturer-Submitted Cost Information (Verbatim)

The cost comparison of Triumeq to its components can be seen in Table 4.

TABLE 4: COST COMPARISON OF TRIUMEQ AND INDIVIDUAL COMPONENTS (TIVICAY AND KIVEXA)

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
DTG/ABC/3TC (Triumeq)	**50 mg/ 600mg/ 300 mg**	**Oral tablet**	**$41.0143**	**Once daily**	**$41.0143**
DTG (Tivicay)	50 mg	Oral tablet	$18.5000	Once daily	$18.50
ABC/3TC (Kivexa)	600mg/ 300mg	Oral tablet	$23.6191	Once daily	$23.6191
Total					**$ 42.1191**

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir.
Note: See Section 6. Current Patent Status for patent expiration date(s).

The price of Triumeq was obtained from ViiV Healthcare and is considered non-confidential. The price of Tivicay (DTG) is the list price submitted to CDR. The price of Kivexa (ABC/3TC) was obtained from Ontario Drug Benefit.

The typical daily drug costs with recommended dosing for Triumeq and Tivicay plus Kivexa are shown in Table 5. The incremental difference with Triumeq reflects a $1.1048 cost savings daily. Moreover, adoption of Triumeq leads to monthly savings of $33.14 and annual savings of $397.73 per patient. When including markup and dispensing fees, the incremental difference calculated is even higher for Triumeq, demonstrating a $535.51 lower annual cost than that of the combination of Tivicay plus Kivexa.

TABLE 5: COST DIFFERENCES OF TRIUMEQ AND ITS COMPONENTS

Drug/Comparator	Tablets per Day	Daily Regimen Cost
DTG/ABC/3TC (Triumeq)	1	$41.0143
DTG (Tivicay) + ABC/3TC (Kivexa)	2	$42.1191
Incremental Difference	**–1**	**–$1.1048**

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir.

Table 6 illustrates the prices for all appropriate comparators.

TABLE 6: COST COMPARISON TABLE

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Drug Cost ($)
DTG/ABC/3TC (Triumeq)	50mg/600mg/ 300 mg	Oral tablet	$41.0143[a]	Once daily	$41.0143
EFV/TDF/FTC (Atripla)	600mg/200mg/ 245mg	Oral tablet	$43.2478[b]	Once daily	$43.2478

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; EFC = efavirenz; FTC = emtricitabine; TDF = tenofovir.
[a] Drug cost provided by ViiV Healthcare.
[b] Drug costs obtained from Ontario Drug Benefit.

5.2 CDR Reviewer Comments

The CDR reviewer noted a few issues for consideration.

As presented in the manufacturer's primary cost comparison analysis (Table 4 in the manufacturer's submission), the DTG/ABC/3TC STR ($41) is cost-saving by $1 per day compared with the sum of the costs of the individual components DTG and ABC/3TC ($42). In the case where the cost of either (or both) individual component(s) is lower in any of the jurisdictions than what is presented in the manufacturer's analysis, the DTG/ABC/3TC STR may be more costly than the concomitant use of the individual components.

As identified by the CDR clinical expert, the DTG/ABC/3TC STR is a reasonable treatment option for patients who have not experienced any viral resistance (e.g., patients who are initiating treatment or switching from other regimens due to issues with tolerability or adherence), and its once-daily dosing regimen may be convenient for patients. As such, the availability of this product may displace the market share of other first-line FDC products. The following DHHS-recommended FDC regimens, which were also considered to be relevant by the CDR clinical expert, would likely be displaced: EFV/TDF/FTC; FTC/rilpivirine (RPV)/TDF; and COBI/EVG/FTC/TDF (Table 7). As reported, the daily cost of the DTG/ABC/3TC STR ($41) is less than other first-line FDC products (daily cost savings ranging from $1 to $5).

While the availability of regimens in co-formulated FDCs offers benefits to patients in terms of convenience and potentially adherence, it presents challenges to generic entrants as individual drug patents expire. For example, the patent for the ABC/3TC FDC (Kivexa) expires in 2018.

TABLE 7: COST COMPARISON TABLE FOR HIV ARV DRUGS IN ADULT PATIENTS — FIXED-DOSE COMBINATIONS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Frequency of Use (/Day)	# Pills (/Day)
Integrase Inhibitor							
DTG/ABC/3TC STR (Triumeq)	**50 mg/600 mg/ 300 mg**	**Tab**	**41.0143**[a]	**1 tablet daily**	**41.01**	**1**	**1**
Nucleoside Analogue Reverse Transcriptase Inhibitors							
EFV/TDF/FTC STR (Atripla)	600 mg/ 300 mg/200 mg	Tab	43.2478	1 tablet daily	43.25	1	1
FTC/RPV/TDF STR (Complera)	200 mg/ 25 mg/300 mg	Tab	42.5305	1 tablet daily	42.53	1	1
COBI/EVG/FTC/TDF STR (Stribild)	150 mg/150 mg/ 200 mg/300 mg	Tab	45.5200	1 tablet daily	45.52	1	1

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; COBI = cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RPV = rilpivirine; STR = single-tablet regimen; TDF = tenofovir.
All prices are from the Ontario Drug Benefit Formulary (accessed January 2015) unless otherwise indicated.
[a] Manufacturer's submitted price.

6. CURRENT PATENT STATUS

6.1 Manufacturer-Submitted Information Regarding Patent Status (Verbatim)

Below are all patents listed on the Patent Register for the components of Triumeq. The information being provided is confidential and not to be released to any third party with the express written consent of GSK (GlaxoSmithKline).

Tivicay (dolutegravir[DTG]):

- Patent pending; will be provided upon availability.

Kivexa (abacavir/lamivudine [ABC/3TC]):

- CA no 1,340,589 … expiry 2016-06-08
- CA no 2,216,634 … expiry 2016-03-28
- CA no 2,289,753 … expiry 2018-05-14

APPENDIX 1: PATIENT INPUT INFORMATION

This section was summarized by CADTH Common Drug Review staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization that addresses access to care, support, and treatment for people living with HIV and hepatitis C. CTAC's organizational goals are to identify, develop, and implement both policy and program solutions through engaging community members, policy-makers, service providers, and other interested stakeholders.

CTAC received unrestricted organizational and educational grants from the following organizations in the 2013-2014 fiscal year: Abbott/AbbVie, Boehringer Ingelheim, Gilead Sciences, Janssen, and ViiV Healthcare. CTAC declared no conflict of interest in the preparation of its submission.

2. Condition and Current Therapy-Related Information

The main source of information was a survey (six HIV-positive persons responded, including one participant involved in the Triumeq clinical trials) in a follow-up to a national consultation webinar on the CDR patient input process and the Triumeq clinical trials. In addition, survey data used in the Tivicay and dolutegravir submissions were also included.

HIV is a life-threatening and serious illness that can compromise the immune system, leaving the patient vulnerable to opportunistic infections. Should these infections overcome the immune system, an AIDS diagnosis is made and death can occur. HIV progression can be effectively controlled through the use of highly active antiretroviral treatment (HAART), which can lead to viral suppression and an undetectable viral load measured by conventional medical technologies. HAART allows people living with HIV to live longer and manage their disease as a chronic illness.

People with HIV face stigma and discrimination associated with this disease, which can manifest itself with negative mental health outcomes or in the form of increased stress. Stress on both personal and social levels can be experienced. Many patients have stress about and long to be "more confident in sexual situations," whereby they would like to not fear infecting their partners. In addition, there can be mental stress associated with their condition, particularly when first diagnosed. Many people living with HIV experience vulnerabilities that affect their social determinants of health (e.g., where they are born or live and how much money they have). Of particular concern to some patients is a lack of nearby medical professionals versed in HIV and its treatment and the travel associated with visiting such specialists and obtaining treatment (e.g., provincial drug plan reimbursements).

Of the six people with HIV who responded to this specific request, the timeline of living with HIV was between four and 29 years, while those on therapy have ranged from four to 15 years. Patients have had experience with Triumeq, Atripla, atazanavir/raltegravir, and darunavir/tenofovir/lamivudine. Most respondents considered their treatment effective as viral loads were controlled to undetectable levels and they presented with limited side effects (especially when compared with older drugs). Some of these side effects were mild diarrhea, mental health concerns, and fatigue. One mildly inconvenient aspect of current treatment is the fact that current treatments necessitate the co-consumption of a meal, even when the patient may not feel hungry.

Caregivers experience significant challenges when caring for those living with HIV, such as "… assistance with navigating the social safety net, acting as a resource person, providing support, transportation to appointments, related costs, and time commitments." There is a desire from caregivers for a "holistic approach" in care that acknowledges the real "challenges related to the social determinants of health." Undue stress is placed on the caregiver as they must develop a varied and complicated skill set by learning intricacies regarding the disease and its episodic nature, its varied treatment, and making sure treatment regimens are followed.

3. Related Information About the Drug Being Reviewed

Five of the six respondents had not been exposed to Triumeq. While some acknowledge the importance of having alternative treatments and that this is a once-a-day treatment, most respondents were satisfied with their current treatment regimen. They indicated that they were pleased with its effectiveness in reducing the viral load and the lack of associated significant side effects. None of the five who were Triumeq-naive indicated that they would make the switch. At least one patient even expressed some trepidation in taking Triumeq due to abacavir sensitivity, which can be associated with cardiologic events (even though this can be screened for); for this reason they would not consider Triumeq. In addition, the single-tablet treatment regimen was not that attractive to these individuals, as they did not have any issues pertaining to the current twice-daily regimen. However, two of these respondents did note that this would be an excellent first-time regimen.

The one respondent who did have experience with Triumeq through a clinical trial did note that it was tolerable and not associated with any side effects, either initially or subsequently. The patient did see the benefit of this new treatment, found it easy to take, and was happy to take it either with or without food. For this person, the effects associated with taking Triumeq were all positive.

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