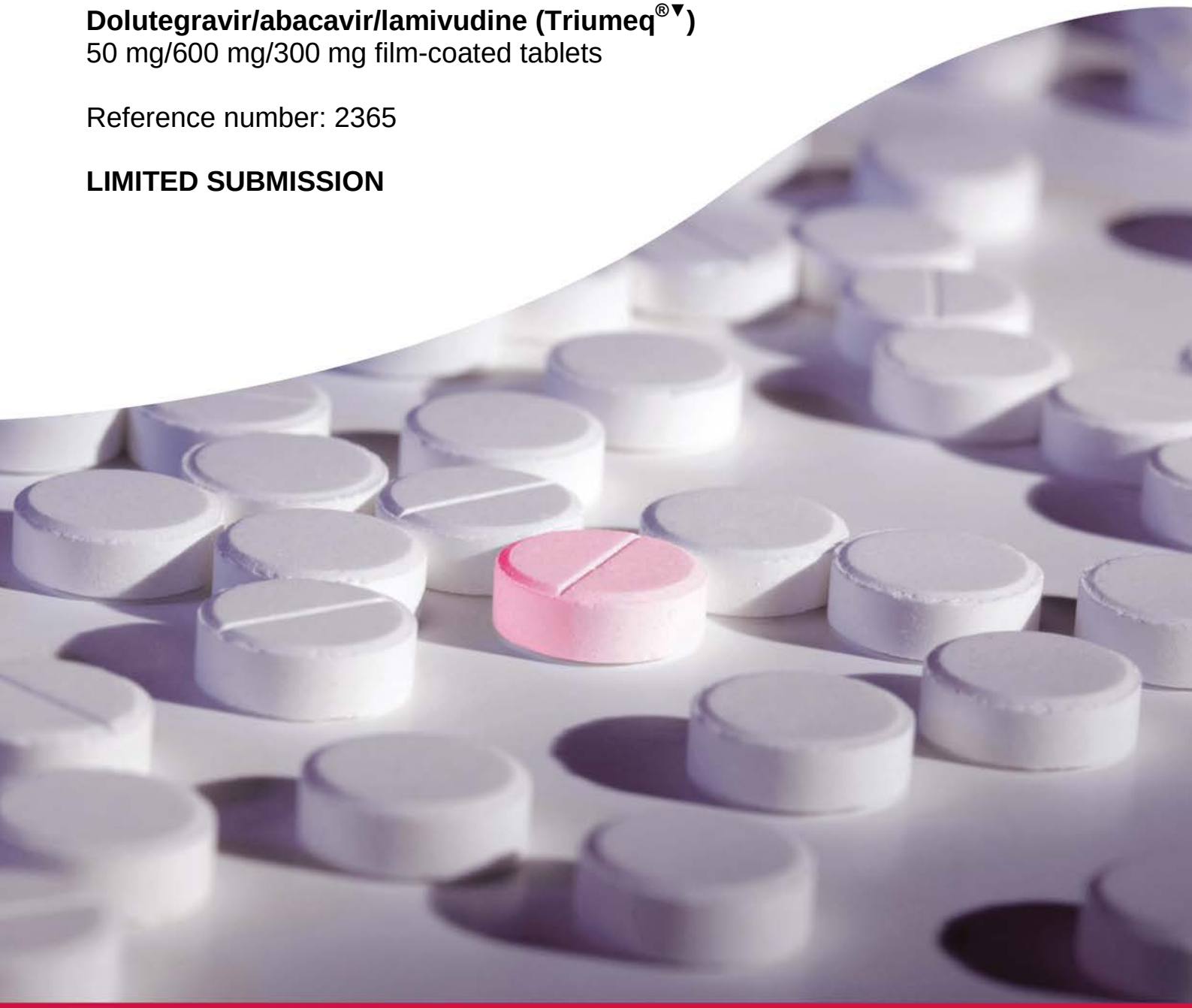
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Dolutegravir/abacavir/lamivudine (Triumeq®▼)
50 mg/600 mg/300 mg film-coated tablets

Reference number: 2365

LIMITED SUBMISSION



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AWMSG Secretariat Assessment Report
Dolutegravir/abacavir/lamivudine (Triumeq®▼)
50 mg/600 mg/300 mg film-coated tablets

This assessment report is based on evidence from a limited submission by ViiV Healthcare UK Ltd on 27 October 2014[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Dolutegravir/abacavir/lamivudine (Triumeq®▼) for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age weighing at least 40 kg[2]. Before initiating treatment with abacavir-containing products, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele[2].
Dosing	The recommended dose of Triumeq®▼ in adults and adolescents is one tablet once daily[2]. Triumeq is a fixed-dose tablet and should not be prescribed for patients requiring dose adjustments. Separate preparations of dolutegravir, abacavir or lamivudine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. In these cases the physician should refer to the individual product information for these medicinal products[2].
Marketing authorisation date	01 September 2014[3]
Comparators	The comparators included in the company submission[1] were: • efavirenz/emtricitabine/tenofovir (Atripla®) • dolutegravir (Tivicay®) + abacavir/lamivudine (Kivexa®) • darunavir + ritonavir + tenofovir/emtricitabine (Truvada®) • darunavir + ritonavir + abacavir/lamivudine (Kivexa®) • raltegravir + tenofovir/emtricitabine (Truvada®) • raltegravir + abacavir/lamivudine (Kivexa®)
Limited submission details	Triumeq®▼ for the above indication met the following criteria for eligibility for a limited submission: • Significant new formulation with a pro-rata or lower cost per treatment. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included a bioequivalence study, NCT01622790 of Triumeq®▼ versus dolutegravir single tablet plus abacavir/lamiduvine fixed-dose combination (FDC) administered separately[1,4]. There are no other studies reported using Triumeq®▼ and all further information on effectiveness and safety are based on the individual components.

The company submission included a phase III, randomised controlled study (SINGLE study) comparing the efficacy and safety of dolutegravir plus abacavir/lamiduvine versus efavirenz/emtricitabine/tenofovir[5]. Two further supporting studies, SPRING-2 and FLAMINGO were also briefly described in the submission[6–8].

2.1 Bioequivalence Study (NCT01622790)

This was a phase I single-centre, randomised, open-label crossover study in healthy adults[4]. Part A compared the bioequivalence of Triumeq®▼ (dolutegravir 50 mg, abacavir 600 mg and 300 mg lamiduvine FDC) with the co-administration of separate tablet formulations of dolutegravir 50 mg and abacavir/lamivudine (600 mg/300 mg) FDC. Part B assessed the effect of food on the bioequivalence of Triumeq®▼[4].

The pharmacokinetic analysis comprised 62 subjects for part A and 12 subjects for part B of the study. Statistical analyses for bioequivalence between the Triumeq®▼ tablet and the dolutegravir and abacavir/lamivudine coadministered tablets showed that the 90% confidence intervals (CI) for the geometric least squares mean ratios of maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) for dolutegravir, abacavir and lamiduvine were all within the 0.80–1.25 bioequivalence criteria[4].

Following administration of Triumeq®▼ with a high fat meal Cmax and AUC were 37% and 48% higher respectively for dolutegravir than in the fasted state and the Cmax for abacavir was 23% lower when administered with food. These results are consistent with results from previous pharmacokinetic studies using the single entity medicines and any differences are not considered clinically significant[4].

2.2 SINGLE study

SINGLE was a multi-centre, phase III, randomised, double-blind study comparing the efficacy and safety of dolutegravir plus abacavir/lamiduvine versus the FDC efavirenz/emtricitabine/tenofovir in anti-retroviral (ART) naive adult patients (n=833)[5]. The primary endpoint was the proportion of patients with a HIV-1 RNA less than 50 copies per mL at week 48 by snapshot analysis. At week 48, 88% of the patients in the dolutegravir plus abacavir/lamiduvine group (364/414) had HIV-1 RNA <50 copies per mL versus 81% in the efavirenz/emtricitabine/tenofovir group (338/419). The adjusted treatment difference between the two groups was 7 percentage points (95% confidence interval, 2–12), these results demonstrated statistical superiority of dolutegravir plus abacavir/lamiduvine over efavirenz/emtricitabine/tenofovir (p=0.003). Secondary endpoints were supportive of the primary endpoint[5]. The SINGLE study was extended to 144 weeks with analysis at 96 and 144 weeks, superiority of dolutegravir plus abacavir/lamiduvine over efavirenz/emtricitabine/tenofovir was maintained at week 144 with 71% versus 63% of patients with HIV-1 RNA <50 per mL respectively (p=0.003)[9–11].

2.3 Supporting studies

Two further studies were briefly referenced in the company submission[1]. SPRING-2 was a multi-centre, phase III, randomised, double-blind study which compared the efficacy of dolutegravir versus raltegravir in ART naive adults, both in combination with an investigator-selected nucleoside reverse transcriptase inhibitor (NRTI) backbone. The primary efficacy endpoint was the same as in the SINGLE study, at week 48 the proportion of patients with HIV-1 RNA <50 copies per mL were 88% in the dolutegravir group and 85% in the raltegravir group. Statistical non-inferiority of dolutegravir over raltegravir was demonstrated[6]. The multi-centre, phase III, open label FLAMINGO study compared the efficacy of dolutegravir versus darunavir plus ritonavir in treatment naive adult patients, once again in combination with an investigator-selected NRTI backbone. At week 48 the proportion of patients with HIV-1 RNA <50 copies per mL

was 90% in the dolutegravir group and 83% in the darunavir plus ritonavir group, superiority was demonstrated[8].

2.4 Safety

All 66 patients enrolled in the bioequivalence study received at least one dose and therefore were included in the safety evaluation[4]. The most commonly reported adverse events (AEs) during part A were nausea, and headache. Tolerability was similar between the two treatments, although the incidence of nausea was higher in the separate entities group (28%) compared to the FDC (15%)[4]. One patient was withdrawn from Part A of the study due to an AE (vomiting) which was considered to be related to Triumeq®▼ administration. No serious AEs and no grade 3 or 4 AEs were observed[4,11,12].

2.5 Points to note

- The All Wales Medicines Strategy Group (AWMSG) has previously issued advice recommending dolutegravir in combination with other anti-retroviral medicines as an option for use in Wales[13].
- The Committee for Medicinal Products for Human Use (CHMP) note that study NCT01622790 was adequately designed and demonstrated bioequivalence of Triumeq®▼ FDC to dolutegravir plus abacavir/lamiduvine. This is crucial in bridging from the separate tablet formulations of dolutegravir plus abacavir/lamiduvine used in the clinical efficacy and safety studies and Triumeq®▼ FDC[12].
- There is no experience with the Triumeq®▼ in HIV-infected patients. CHMP note that the safety profile of Triumeq®▼ is expected to be consistent with the single agents, no additional risks or safety issues have been identified due to the combination therapy[12].
- On the basis of feedback from an advisory panel in Wales the applicant company indicate that the majority (70-80%) of anti-retroviral therapy (ART) naive patients receive efavirenz/emtricitabine/tenofovir (Atripla®)[1].
- The company submission did not include any evidence for use in ART experienced patients[1]. SAILING was a study conducted in integrase inhibitor (INI) naive patients resistant to two or more classes of ART, superiority of the dolutegravir regimen over raltegravir was demonstrated[14].
- The once-daily, single tablet regimen may be more convenient and increase compliance compared to regimens requiring multiple pills per day. CHMP noted that as Triumeq®▼ does not need to be taken with food (in contrast to darunavir) or on an empty stomach (in contrast to Atripla®) and a lack of CYP3A4 interactions may confer additional benefits[12].
- Triumeq®▼ is not recommended in patients with integrase inhibitor resistance, as the recommended dose of dolutegravir in this group of patients is 50 mg twice daily and Triumeq®▼ contains only a once daily dose of 50 mg. Likewise, for patients prescribed efavirenz, nevirapine, tipranavir/ritonavir and rifampicin the recommended dose of dolutegravir is 50 mg twice daily and therefore Triumeq®▼ should not be prescribed[2].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

Based on 2013 figures from Public Health England the company estimate that in 2014 there are 1793 patients with HIV in Wales, of these 85.5% receive ART and therefore 1533 patients are eligible for treatment[1,15].

The forecasted figures for the uptake of Triumeq®▼ are shown in table 1 below, the company estimates 20% of patients already receiving ART will switch to Triumeq®▼.

The cost of Triumeq®▼ with a Wales Patient Access Scheme (WPAS) is [commercial in confidence removed][1].

Table 1 Five-year forecast for uptake of Triumeq®▼[1]

	Year 1 (2015)	Year 2 (2016)	Year 3 (2017)	Year 4 (2018)	Year 5 (2019)
New patients	56	85	115	133	139
Total patients	56	141	256	389	528
Annual cost with WPAS	¶¶	¶¶	¶¶	¶¶	¶¶

WPAS: Wales Patient Access Scheme
¶¶ commercial in confidence data removed

3.1.1 AWTTC critique

- The prevalence and incidence population figures provided for HIV patients are obtained from Public Health England surveillance data for England and Wales and is the most accurate estimation of patient numbers available[15].
- Although mortality figures were not taken into account when estimating the prevalent population of patients with HIV in Wales any overestimation is likely to be small, deaths in 2013 totalled 13[15].
- The five-year forecast for uptake of Triumeq®▼ is based on assumptions and estimations and therefore is subject to uncertainty[1].

3.2 Comparative unit costs

For comparison the company has provided figures for the monthly cost of the single entity dolutegravir in combination with an NRTI backbone of either Truvada® or Kivexa®[1]. The cost of Atripla® has also been included as it is the most frequently prescribed FDC in Wales for the indication under consideration[1]. A Wales Patient Access Scheme (WPAS) is in place for dolutegravir and the same scheme is in place for Triumeq®. The figures are shown in table 3 below and include the WPAS discount.

Table 3. Monthly cost for Triumeq and its comparator treatments for HIV in Wales

	Example dose	Monthly cost with WPAS*
Triumeq®▼	Dolutegravir 50 mg/abacavir 600 mg/lamiduvine 300 mg od	¶¶
Tivicay®▼ + Kivexa®	Dolutegravir 50 mg od + abacavir 600 mg/lamiduvine 300 mg od	¶¶ (dolutegravir) + £299.41 (Kivexa®)† ¶¶ (total)
Doultegravir 50 mg + Truvada	Dolutegravir 50 mg od + tenofovir 245 mg/emtricitabine 200 mg od	¶¶ (dolutegravir) + £418.50 (Truvada®)† ¶¶ (total)
Atripla®	Efavirenz 600 mg/emtricitabine 200 mg/tenofovir 245 mg od	£532.87†

od: once daily; WPAS: Wales Patient Access Scheme
*Cost is based on 30 day cost.
†British National Formulary list price[16]
¶¶ commercial in confidence data removed

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, dolutegravir/abacavir/lamivudine Triumeq®▼ is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that dolutegravir/abacavir/lamivudine Triumeq®▼ may be supplied by a home healthcare provider. The applicant company notes that the homecare companies will have access to the WPAS price.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 20 November 2014.
Date range of evidence search: No date limits were applied to database searches.

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