Scottish Medicines Consortium

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NHS SCOTLAND

emtricitabine/tenofovir disoproxil 200mg/245mg film-coated tablets (Truvada®) 　　　　　　　　　　　　　　　　　　　　　**SMC No. (1225/17)**

Gilead Sciences Ltd

10 March 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

emtricitabine/tenofovir disoproxil (Truvada®) is accepted for use within NHS Scotland.

Indication under review: In combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

In the pivotal studies conducted in men who have sex with men (iPrEx) and heterosexual couples, one of whom was HIV negative (Partners PrEP), there were statistically significant relative reductions in incidence of HIV for emtricitabine/tenofovir disoproxil compared with placebo.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.[1]

Dosing Information

Emtricitabine 200mg/tenofovir disoproxil 245mg, one tablet, orally with food once daily.

Emtricitabine/tenofovir disoproxil should be initiated by a physician experienced in the management of HIV infection.[1]

Product availability date

18 August 2016

Summary of evidence on comparative efficacy

Emtricitabine is a nucleoside analogue of cytidine, and tenofovir is a nucleoside monophosphate analogue of adenosine monophosphate; both have activity specific to human immunodeficiency virus (HIV)-1, HIV-2 and hepatitis B virus (HBV).[1] Emtricitabine/tenofovir disoproxil, a fixed dose combination tablet, has been licensed for the treatment of HIV-1 infected adults (as combination antiretroviral therapy [ART]) since 2005 and was accepted for use by SMC for this indication in 2006 (SMC 237/06). The current submission concerns the use of once daily emtricitabine/tenofovir disoproxil in combination with safer sex practices for pre-exposure prophylaxis (PrEP) in adults at high risk. It is currently the only preparation licensed for PrEP.

Evidence of efficacy comes from two pivotal multi-centre, placebo-controlled, phase III studies, iPrEx (CO-US-104-0288) conducted in men who have sex with men (MSM) and Partners PrEP (CO-US-104-0380) conducted in heterosexual couples where one partner was HIV-1 negative and the other was not (HIV-1 serodiscordant couples).[2,3]

The iPrEx study recruited 2,499 people from South America, USA, South Africa and Thailand who were of male sex at birth, aged ≥18 years, HIV negative and had evidence of high risk for HIV infection. High risk was defined as any of the following in the six months prior to screening: anal sex with at least four male partners (at least six in some countries), diagnosis of a sexually transmitted infection (STI), history of transactional sex activity or unprotected anal intercourse with a partner who was HIV infected or of unknown infection status. Participants were randomised equally to daily emtricitabine/tenofovir disoproxil 200mg/245mg or placebo; in addition, all received HIV prevention services which included risk-reduction counselling, condoms, and diagnosis and treatment of symptomatic STI.

The Partners PrEP study recruited 4,758 heterosexual couples from Kenya and Uganda. HIV-1 seronegative partners were aged 18 to 65 years and sexually active (defined as at least six episodes of vaginal intercourse with the HIV-1 seropositive study partner in the previous three months and planned to remain in the relationship for the study period). HIV-1 seronegative participants were randomised equally to daily emtricitabine/tenofovir disoproxil 200mg/245mg, tenofovir disoproxil 245mg (not licensed for PrEP, and not discussed further) or placebo; in

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addition all received HIV prevention services. These included HIV-1 testing with counselling, individual and couples risk-reduction counselling, screening and treatment for STI, condoms and referral for male circumcision and post exposure prophylaxis according to national policies.

The primary analysis of efficacy in both studies was based on the incidence of HIV infection in the modified intent-to-treat (mITT) analysis set which excluded participants who were infected with HIV at enrolment. The efficacy measure was the relative effectiveness, and both studies were powered to show at least 30% efficacy. In iPrEx at the 1 May 2010 cut-off (primary analysis), there were 3,324 person-years of follow up. In Partners PrEP, the study was discontinued as predetermined stopping rules were met due to the strong trend for HIV-1 protection in participants treated with PrEP; at the 10 July 2011 cut-off (interim review), there were 7,830 person-years of follow up. Results are included in table 1. Treatment with emtricitabine/tenofovir disoproxil compared with placebo significantly reduced the number of HIV infections; however, in the iPrEx study, the null hypothesis of ≤30% efficacy could not be rejected as the lower bound of the confidence interval was 15%.

Table 1: results of primary endpoint for iPrEx and Partners PrEP studies (mITT)

	emtricitabine/tenofovir disoproxil	placebo	Risk reduction (95% CI), p-value
iPrEx	N (mITT)=1,224	N (mITT)=1,217	
Number of HIV infections	36	64	44% (95% CI: 15% to 63%), p=0.005
Rate/100 person-years	NR	NR	
Partners PrEP	N (mITT)=1,568	N (mITT)=1,568	
Number of HIV infections	13	52	75% (95% CI: 55% to 87%), p<0.001
Rate/100 person-years	0.50	1.99	

mITT=modified intention to treat; NR=not reported; CI=confidence interval

In pre-specified subgroup analyses of iPrEx, in participants who reported unprotected receptive anal intercourse (URAI), the relative reduction in incidence of HIV was 58% (95% CI:32% to 74%). A pre-specified subgroup analysis was performed to investigate whether drug levels correlated with protective effect. At least one of the study drug components was detected in 8.8% (3/34) of emtricitabine/tenofovir disoproxil-treated participants with HIV seroconversion, compared with 51% (22/43) of emtricitabine/tenofovir disoproxil-treated participants without HIV seroconversion (matched controls); relative reduction in incidence of HIV was 92% (95% CI: 40% to 99%), p<0.001.[2] In an updated analysis (mITT) with 4,237 person-years of follow-up, results of the primary endpoint were similar to the primary analysis; 48 versus 83 HIV infections, relative reduction in incidence of HIV, 42% (95% CI: 18% to 60%), p=0.002.[1] The rate per 100 person-years was 2.4 for emtricitabine/tenofovir disoproxil and 4.2 for placebo.[4]

In the iPrEx study, sexual practices were similar in the two groups at all timepoints. There were reductions in total numbers of sexual partners with whom the respondent had receptive anal intercourse and the percentage of those whose partners who used a condom increased. In addition, there were no significant between-group differences in the numbers of participants with STI during follow up. In Partners PrEP, the proportion of participants who reported having sex without a condom with their HIV-1-seropositive partner reduced from baseline to month 12 and

was similar between groups. Also, the proportions of HIV-1 seronegative participants with STI were similar between groups.[3]

Participants who had previously enrolled in the iPrEx study or two other studies could enter a 72-week open-label extension cohort study where participants could choose to commence PrEP at any point up to week 48. A total of 1,603 HIV-negative people were recruited, of whom 76% (1,225/1,603) received emtricitabine/tenofovir disoproxil. HIV incidence was 1.8 per 100 person-years in participants receiving PrEP compared with 2.6 per 100 person-years in participants who chose not to commence PrEP and 3.9 per100 person-years in the placebo group of the previous randomised phase.[5]

At the time of the interim analysis of the Partners PrEP study, participants who received placebo were offered re-randomisation to emtricitabine/tenofovir disoproxil or tenofovir disoproxil, and those who previously received active treatment continued on this. Of the 1,584 HIV-1 seronegative placebo-treated participants, 1,418 were eligible for re-randomisation and 1,264 were re-randomised. The updated analysis included an additional 3,569 person-years of follow up; median follow up was 35.9 months for participants receiving active treatment at initial randomisation and 12 months for those participants who were re-randomised from the placebo group. There were 26 additional HIV-1 infection endpoints. HIV seroconversion occurred in 52 participants; 21 in the emtricitabine/tenofovir disoproxil group (and 31 in the tenofovir disoproxil group). The rate per 100 person-years was 0.48 for emtricitabine/tenofovir disoproxil.[6]

Supportive data come from PROUD, a pilot phase, randomised, open-label study conducted in 544 participants attending sexual health clinics in England. Participants were of male sex at birth, aged ≥18 years, HIV negative and reported unprotected anal intercourse in the previous 90 days and were likely to have unprotected anal intercourse in the next 90 days. This study was intended to mimic real life, with lack of a screening visit and the use of HIV and STI results collected at other clinics and during non-study visits. Participants were randomised equally to daily emtricitabine/tenofovir disoproxil 200mg/245mg starting at enrolment (immediate group) (n=275) or daily emtricitabine/tenofovir disoproxil 200mg/245mg deferred for one year (deferral group) (n=269). All participants were offered interventions to reduce risk according to routine practice at the recruiting clinic as well as HIV testing and STI screening. The aim of the pilot phase was to assess recruitment and retention and to test the feasibility of a large-scale study. An interim analysis in October 2014 led the principal investigators to offer emtricitabine/tenofovir disoproxil to the deferred group. At this interim analysis in the immediate group, there were 243 person-years of follow up and in the delayed group 222 person-years follow up.[7]

The number of new incident HIV infections was three in the immediate group and 20 in the deferred group; relative reduction in incidence of HIV 86% (90% CI 64% to 96%), p=0.0001. Of the HIV infections in the immediate group, one infection was considered to have predated PrEP treatment and the others occurred in participants where adherence was uncertain. The incidence of HIV infection was estimated to be 1.2 per 100 person-years in the immediate group and 9.0 per 100 person-years in the deferred group. The proportion of participants who reported unprotected anal intercourse with at least 10 partners was 21% in the immediate group and 12% in the deferred group (p=0.03, test for trend). There were no differences between groups for total number of different anal partners at one year, though these varied widely at enrolment, and the one year visit and incidences of STI were similar between groups.[7]

Additional supportive data are from CDC TDF2 which recruited sexually active heterosexuals aged 18 to 39 years from Botswana. Participants were randomised equally to daily emtricitabine/tenofovir disoproxil 200mg/245mg or placebo, stratified by site and sex; in addition

participants received HIV prevention services, which included counselling on risk reduction, free male and female condoms, and screening and treatment of STIs.

The study was halted following recruitment of 1,219 participants, despite the total sample required to maintain 80% power being re-calculated as 2,500 due to higher than expected loss to follow up. Participants were followed up for 1,563 person-years (median 1.1 years; maximum 3.7 years). A total of 601 and 599 participants were followed-up for seroconversion in the emtricitabine/tenofovir disoproxil and placebo groups, respectively. The number of new incident HIV infections in the mITT population was nine in the emtricitabine/tenofovir disoproxil group and 24 in the placebo group; relative reduction in incidence of HIV 62%; 95% CI: 22% to 83%; p=0.03. The incidence of HIV infection was estimated to be 1.2 per 100 person-years for emtricitabine/tenofovir disoproxil and 3.1 per 100 person-years for placebo.[8]

The ANRSIPERGAY study investigated on-demand (off-label) use of emtricitabine/tenofovir disoproxil in MSM aged ≥18 years at high risk for HIV infection, defined as a history of unprotected anal intercourse with at least two partners during the previous six months. There was a significant relative reduction in incidence of HIV for on-demand emtricitabine/tenofovir disoproxil compared with placebo.[9]

Summary of evidence on comparative safety

In iPrEx and Partners PrEP, any adverse event, serious adverse events and grade 3 or 4 adverse events were reported in similar proportions of participants in the emtricitabine/tenofovir disoproxil and placebo groups.

In iPrEx, serum creatinine 1.1 times upper limit of normal (ULN) or 1.5 times baseline value occurred in 2.0% of participants in the emtricitabine/tenofovir disoproxil group and 1.1% in the placebo group. There were 10 elevations of serum creatinine resulting in study medicine discontinuation (seven in the emtricitabine/tenofovir disoproxil group and three in the placebo group), and in nine participants, study medicine was restarted. In the emtricitabine/tenofovir disoproxil and placebo groups, nausea of ≥ grade 2 occurred in 1.6% and <1%, and unintentional weight loss (≥5%) in 2.2% and 1.1% of participants respectively (p=0.04 for both). Other adverse events including headache, depression, diarrhoea and bone fracture occurred in similar proportions across the two groups (and incidences were <5%).[2]

In the open-label extension cohort study, the most common symptoms resulting in interruption of emtricitabine/tenofovir disoproxil treatment were gastrointestinal, such as nausea or abdominal pain. Serum creatinine concentration increases (all grade 1) occurred three times; all returned to baseline on treatment interruption and none recurred after restarting treatment.[5]

In Partners PrEP, there were no significant differences in the frequency of serum creatinine or phosphorus abnormalities between the emtricitabine/tenofovir disoproxil and placebo groups. In the emtricitabine/tenofovir disoproxil and placebo groups, decreased absolute neutrophil count occurred in 18% and 13% of participants respectively (p<0.001). Cellulitis and hypertension occurred in a lower proportion of participants in the emtricitabine/tenofovir disoproxil group (0.8% and 0.9%) than in the placebo group (1.6% and 1.9%). Other adverse events occurred in similar proportions across the two groups and incidences were <5% except for malaria, upper respiratory tract infection, respiratory tract infection and urinary tract infection.[3] With longer term follow up,

the frequency of adverse events overall in participants treated with emtricitabine/tenofovir disoproxil was similar to that in the placebo group up to the interim analysis.[6]

In PROUD, the most common treatment-related adverse events were nausea, headache and arthralgia. Three participants interrupted treatment due to raised creatinine concentration, with one considered probably related, one possibly related and one unlikely to be related to study treatment. No serious adverse events (29 events in 27 participants) were considered to be treatment-related.[7]

Summary of clinical effectiveness issues

Between 2011 and 2015 inclusive there were 1,796 HIV infections reported in Scotland; MSM accounted for 47% of these and heterosexual acquired HIV accounted for 38%.[10] Prevention strategies and programmes currently include early diagnosis of HIV infection, ART for those diagnosed HIV positive to reduce the risk of onward transmission, post-exposure prophylaxis after sexual exposure (PEPSE) and advice on condom use.[11] Emtricitabine/tenofovir disoproxil is the first preparation to be licensed for PrEP. Clinical experts consulted by SMC considered that there is unmet need for effective HIV prevention strategies and they believed this should include PrEP.

iPrEx conducted in MSM, and Partners PrEP in HIV-1 serodiscordant heterosexual couples were the pivotal studies comparing emtricitabine/tenofovir disoproxil with placebo.[2,3] Supportive data come from PROUD (an open-label pilot phase study) and CDC TDF2 (conducted in heterosexual participants).[7,8] In all studies, participants also received HIV prevention strategies, and there were statistically significant relative reductions in incidence of HIV for emtricitabine/tenofovir disoproxil compared with placebo or no treatment. In iPrEx, a relative reduction in incidence of HIV of <30% could not be ruled out, but in the subgroup who reported URAI, the relative reduction in incidence of HIV was 58% and efficacy of at least 30% was demonstrated.

In iPrEx, high-risk behaviour reported by participants decreased substantially after enrolment and was lower than baseline during the study, and in Partners PrEP the proportion of participants who reported having sex without a condom decreased. Also, the proportions of participants who had an STI whilst on study did not differ between the emtricitabine/tenofovir disoproxil and placebo groups.[2,3] However, in the PROUD study, the proportion of participants who reported unprotected anal intercourse with at least 10 partners was higher in the immediate than deferred group (21% versus 12%). In this study there are no longitudinal data on sexual behaviour and data on risk compensation are limited to the one year time point.[7]

In the iPrEx study, while reported tablet use was high, results of drug exposure (by intracellular assay) suggested lower adherence.[2] In the Partners PrEP study, serodiscordant couples were recruited, HIV infection status within couples was known and the partners' engagement in treatment may have assisted adherence.[12] In the PROUD study, there are no data on adherence, although all 52 participants who were sampled and reported treatment adherence had detectable tenofovir levels.[7] It has been noted that placebo-controlled studies may underestimate adherence in clinical practice because there is less incentive to take a tablet which may be placebo.[2,7] Results of studies including Partners PrEP and iPrEx indicate a strong association between adherence and protection. However, longer-term adherence to the once daily regimen of emtricitabine/tenofovir disoproxil is not known.[13]

The Partners PrEP study was stopped early as the predetermined stopping rules were met with the demonstration of HIV-1 protection from PrEP.[3] The CDC TDF2 study was underpowered; the 1,563 person-years follow up represented 80% of the person-years that was estimated to be required for the power calculation.[8] PROUD was stopped early, after the pilot phase, due to the benefit observed in the immediate compared with deferred group.[7]

There were variations in the populations recruited to the iPrEx and PROUD studies. The iPrEx study was conducted in South America, USA, South Africa and Thailand, whereas PROUD was conducted in sexual health clinics in England; the latter study is likely to be of more relevance to a Scottish population. Furthermore, the definitions of high risk varied between the studies and the incidence of HIV infection in the control groups differed two-fold; 4.2 and 9.0 per 100 person-years.[2,7] Sexual risk behaviour in PROUD was noted to be diverse and HIV infection rate in the deferred group (9.0 cases per 100 person-years) was higher than the national average of 1.34 cases per 100 person-years reported in 2012 in men attending sexual health clinics in England. The authors of the study publication suggested that the population recruited to PROUD was highly selected, and that the offer of PrEP appeals to men who are most likely to benefit from it.[7] Participants in the deferred group may have accessed PrEP from alternative sources (or indeed enrolled twice to the study, as was detected for two participants) which could have resulted in the effectiveness of emtricitabine/tenofovir disoproxil being underestimated.[7]

There are limitations with the populations recruited to the heterosexual studies; all were conducted in African countries, restricting their generalisability to a Scottish population. Furthermore, in the Partners PrEP study, HIV-1 seropositive partners recruited to the study were not receiving ART, whereas in Scottish clinical practice most would be eligible for ART. Levels of risk for HIV infection in participants varied across the studies. HIV infection rates in the control groups in these studies were 1.99 to 3.1 per 100 person-years and it is not known whether these are reflective of risk of HIV infection in heterosexuals in Scotland at high risk and eligible for PrEP.[3,8]

The ANRS IPERGAY study, which investigated on-demand use of PrEP, has limited applicability to the licensed treatment regimen currently under review.[9] The European Medicines Agency noted that two further studies conducted in heterosexual females in South Africa, Kenya and Tanzania (FEM PrEP) and South Africa, Uganda and Zimbabwe (VOICE [MTN-003]) showed no benefit for emtricitabine/tenofovir disoproxil compared with placebo. However, poor treatment adherence was noted in these studies.[12-14]

There is a risk of clinically important resistance to emtricitabine/tenofovir disoproxil developing in a person who becomes HIV positive whilst on PrEP.[13,15] The summary of product characteristics advises that whilst on emtricitabine/tenofovir disoproxil for PrEP frequent HIV testing (at least every three months) should be undertaken using a combined antigen/antibody test. Furthermore, emtricitabine/tenofovir disoproxil for PrEP should not be commenced if there is suspicion of acute infection.[1]

No new adverse reactions to emtricitabine/tenofovir disoproxil were identified from the iPrEx and Partners PrEP studies, where participants were followed for a median of 71 weeks and 87 weeks, respectively. Small decreases in bone mineral density were observed in studies of PrEP. Renal effects of tenofovir are considered to be unlikely, as people who will be eligible for PrEP will have low rates of factors (such as, age, lower creatinine clearance, diabetes and concomitant renal toxic medicines) associated with renal abnormalities. However, the benefit-risk relationship is of importance when considering emtricitabine/tenofovir disoproxil to prevent HIV infection, as non-pharmacological approaches are also available. Furthermore, people who are started on

emtricitabine/tenofovir disoproxil for PrEP should be counselled to adhere strictly to the recommended dosing.[1,13]

Clinical experts consulted by SMC considered that emtricitabine/tenofovir disoproxil is a therapeutic advancement as it is the first medicine to be licensed for PrEP and is effective in reducing HIV acquisition. Its place in therapy would be in high-risk patients, including those who have required treatment for a rectal STI or disclosed URAI. Prescribing would be from sexual health clinics.

Summary of comparative health economic evidence

The submitting company presented economic analyses comparing emtricitabine/tenofovir disoproxil in combination with safer sex practices to safer sex practices alone. The company provided cost-effectiveness analyses (CEA) using both 'cases of HIV-1 infection prevented' and 'life years gained' as the outcome measures. A cost-utility analysis (CUA) was also provided, with quality adjusted life years (QALYs) as the outcome of interest. All analyses were presented across different patient populations with differing levels of baseline risk of HIV-1 infection: MSM, high risk heterosexuals and heterosexuals with a serodiscordant partner. The time horizon for the analysis was stated as being lifetime. The company presented all analyses in terms of the impacts from '100 person years of treatment' and as such does not make any assumptions regarding the duration of treatment for patients. All analyses presented below assumed once daily dosing.

In terms of the effectiveness data used in the economic analyses, the submitting company assumed that emtricitabine/tenofovir disoproxil would result in an 86% reduction from baseline in newly acquired HIV-1 infections in all the patient populations considered (on the basis of the findings from the PROUD and ANRS IPERGAY studies).[7,9] This rate of reduction was applied to the base line levels of infection in the control arms of the studies for each population. To calculate the life years gained, it was assumed that each case of HIV-1 infection prevented would result in a gain of 7.5 years (undiscounted), and to calculate the QALYs in the cost-utility analysis, each of these life years gained was at a quality of life score of 0.89. No difference in quality of life was assumed between arms of the model other than in the life-extension phase. No differences in rates of sexually transmitted infections, risk behaviours or adverse events were assumed in the analysis.

Conservatively, the analysis did not include any effects on potential reduction in the use of current post-exposure prophylaxis. Other costs in the analyses related to costs associated with additional monitoring while on treatment, and the costs associated with the lifetime care of a patient who developed HIV-1 infection. The latter was taken from a published study in the MSM population which estimated a lifetime cost of £185k.[16]

The results of the CEA using cases prevented as the outcome are shown in table 2 below.

Table 2: Results of the CEA using cost per infection prevented

Infection rate per 100 person-years			Cost per 100 person-years			Cost per HIV-1 infection prevented
Baseline	TVD	Difference	Offset costs, HIV-1 prevention	TVD, annual cost	Total cost	
MSM						
	1.3	–7.7	–£1,433,448	£462,522	–£970,926	**Dominant (cheaper, more effective)**
9.0						
6.6	0.9	–5.7	–£1,051,195	£462,522	–£588,673	**Dominant**
4.3	0.6	–3.7	–£684,870	£462,522	–£222,347	**Dominant**
High risk heterosexual adults						
3.1	0.4	–2.7	–£493,743	£462,522	–£31,221	**Dominant**
Serodiscordant heterosexual couples						
2.0	0.3	–1.7	–£318,544	£462,522	£143,978	£83,708

TVD=Truvada® (emtricitabine/tenofovir disoproxil)

The results in terms of the CEA using life years gained and the CUA are shown in table 3 below:

Table 3: Results of CEA and CUA

Baseline rate of infection	TVD rate of infection	Difference in infection rate	Total cost	Life years gained	Cost per life year gained	QALY	ICER
MSM							
9.0	1.3	–7.7	–£970,926	14.63	**Dominant**	13.02	**Dominant**
6.6	0.9	–5.7	–£588,673	10.73	**Dominant**	9.55	**Dominant**
4.3	0.6	–3.7	–£222,347	6.99	**Dominant**	6.22	**Dominant**
High risk heterosexual adults							
3.1	0.4	–2.7	–£31,221	5.04	**Dominant**	4.48	**Dominant**
Serodiscordant heterosexual couples							
2.0	0.3	–1.7	£143,978	3.25	£44,290	2.89	£49,764

TVD=Truvada® (emtricitabine/tenofovir disoproxil)

The company's base case results showed that treatment would be considered cost-effective in all populations apart from serodiscordant heterosexual couples (because of their lower levels of base line risk of infection).

The company provided a range of one-way sensitivity analyses for each set of results varying parameters such as the risk reduction, cost associated with treating an HIV case and the utility

value. For the MSM population, the sensitivity analyses shown that emtricitabine/tenofovir disoproxil remained dominant. In the serodiscordant heterosexual and heterosexual adult populations, the results of the key sensitivity analyses are shown in table 4 below in terms of the cost per QALY results:

Table 4: Results of key sensitivity analyses

Sensitivity analysis conducted	Results (cost per QALY)- heterosexual adults	Results (cost per QALY)- serodiscordant heterosexual adults
Efficacy of 75%	£8,165	£73,211
Lifetime cost of HIV-1 infection reduced to £148k	£15,058	£71,784
Life years gained per case of HIV-1 infection avoided reduced to 7 years	dominant	£62,205
Utility value in additional life years reduced to 0.72	dominant	£62,205

The company also presented sensitivity analysis to show the impact of using an intermittent dosing regimen rather than daily dosing; however, as this is not within the licence, it is not presented here.

There were a number of limitations or weaknesses with the analyses:

- An important issue with the analysis relates to the use of the '100 person years of treatment' to structure the model findings. This meant that the analysis was not informative about the impact of different patient treatment durations : it could be interpreted that the analysis as presented sets out the cost-effectiveness of one year of treatment in 100 patients (e.g. to coincide with a period of high risk behaviour in an individual's life), or as the cost-effectiveness in a group of individuals taking treatment for different treatment durations (e.g. 10 people taking treatment for one year, 20 people taking treatment for 2 years plus 10 people receiving treatment for 5 years). Thus, the modelling approach was simplistic and not able adequately to take account of variation over time, for example in terms of treatment costs (including discounting of treatment costs), baseline risks or effects.
- The company assumed that a reduction of 86% in the risk of baseline infection and applied this to all the subgroups presented. However, the risk reductions seen in the pivotal studies were smaller than this. The company did provide additional analysis using the effectiveness estimates from each individual study directly, and this had an impact on the results. For example, the cost per QALY in one of the MSM groups changed from dominant to £35k and from dominant to £33k in heterosexuals, and increased from £49k to £73k in serodiscordant heterosexual couples. While there may be issues about generalisability of the findings from some of the studies to the Scottish population, this analysis was helpful in highlighting the sensitivity of the results to lower effectiveness rates. Related to these findings, the clinical studies showed that a key determinant of treatment effectiveness was the degree of treatment adherence. This was not addressed in sensitivity analysis directly (given the simplicity of the company model) but, as can be seen from the impact of assuming lower effectiveness, lower rates of treatment adherence in practice could have considerable impact on the cost-effectiveness results.

- The results showed sensitivity to the predicted life year gained associated with each case of infection prevented. This was estimated from UK population life expectancy data. However, as life expectancy in the Scottish population is lower than the UK as whole, the assumed life year gain may not be as high as assumed in the base case.
- The results showed sensitivity to the utility value assumed for the life years predicted to be gained. The company noted that these life years would occur approximately 40 years in the future when individuals would be in their 70s. As health related quality of life has been shown to decline with age, the use of a value of 0.89 for these years is an overestimate, and the value used in sensitivity analysis of 0.71 is more reflective of population norms for this age group.
- Additional monitoring costs while on treatment were assumed, but the analysis did not assume any costs associated with treatment initiation e.g. clinic visits, counselling etc. SMC clinical experts have indicated that it would be reasonable to expect some additional service costs as a consequence of offering treatment.
- The New Drugs Committee had concerns around the levels of baseline risk of infection used to model the high risk heterosexual adult population in terms of its relevance to the Scottish population. As such, there were concerns about the robustness of the cost-effectiveness results in this group.

The company provided an analysis which combined a number of these sources of uncertainty in sensitivity analysis (ie used a utility value of 0.71, included a treatment-initiation cost and used a lower life year gain estimate of 7), alongside varying estimates of treatment effectiveness. Using the effectiveness results from each individual study directly in this combined analysis resulted in emtricitabine/tenofovir disoproxil remaining dominant in the MSM population unless the infection rate was assumed to reduce from 4.3 cases per 100 person years to 2.4 with emtricitabine/tenofovir disoproxil (modified ITT data from iPrEX), when the cost per QALY changed from dominant to £59,480. The figures in the heterosexual population and the serodiscordant heterosexual populations increased to £55,597 and £113,537 respectively in these combined analyses. If the efficacy rate was set at 75% for all subgroups, emtricitabine/tenofovir disoproxil remained dominant in the MSM groups and had costs per QALY of £20,957 and £113,537 in the heterosexual adult and serodiscordant heterosexual couples respectively. At the base case assumption of 86% effectiveness in all subgroups, treatment was dominant in the MSM and heterosexual adult population but had a cost per QALY of £80,165 in the serodiscordant heterosexual population.

The pattern of results suggests that the cost-effectiveness case was more robust in the MSM population unless low rates of baseline risk and lower levels of treatment effect existed, but that the results in the high risk heterosexual adult and serodiscordant heterosexual adult populations were associated with greater uncertainty and higher ICERs.

Despite these issues, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- We received a joint patient group submission from: HIV Scotland, Waverley Care, Terrence Higgins Trust and the National AIDS Trust (NAT). All four are registered charities.

- HIV Scotland has received 6.8% pharmaceutical company funding in the past two years, including from the submitting company. Waverley Care has received 1.7% pharmaceutical company funding in the past two years, including from the submitting company. Terrence Higgins Trust has received 0.54% pharmaceutical company funding in the past two years, including from the submitting company. The National AIDS trust has received 15.5% pharmaceutical company funding in the past two years, including from the submitting company.

- People vulnerable to HIV must constantly be aware of their own risks and negotiate related social situations. Relentlessly managing the risk of HIV has a detrimental effect on mental health and the way people feel about sex. Nearly half of people are diagnosed late in Scotland. Late diagnosis, and poor health associated with HIV can put significant financial burdens on individuals and their families.

- Current prevention methods have not been able to reduce the number of new diagnoses of HIV in Scotland in the past ten years.

- PrEP provides an opportunity for expanding existing prevention methods and creating a comprehensive package that will be better able to meet the needs of people vulnerable to HIV. It was suggested that availability of PrEP on the NHS would remove the stigma that people taking, or wanting to take, PrEP are currently facing, and that having to fund PrEP independently exacerbates inequalities in health.

Additional information: guidelines and protocols

British HIV Association/British Association for Sexual Health and HIV issued a second update on their position statement on PrEP in UK, in May 2016.[17]It states that PrEP should be available to the following groups in conjunction with a comprehensive HIV prevention package; MSM, transgender men and transgender women who are engaging in condomless anal sex; HIV-negative partners who are in serodifferent heterosexual and same-sex relationships with a HIV-positive partner whose viral replication is not suppressed; and other heterosexuals considered to be at high risk.

European AIDS Clinical Society published guidelines, version 8.1, in October 2016.[18]These recommend use of PrEP for HIV-negative MSM and transgender individuals when condoms are not used consistently with casual partners or with HIV-positive partners who are not on treatment. It may be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and have multiple sexual partners where some of whom are likely to have HIV infection and not being on treatment.

Scottish Health Protection Network published PrEP in Scotland on behalf of the Scottish HIV PrEP short life working group, in October 2016.[19]This considered that PrEP should be available to people with greatest risk of acquiring HIV if aged 16 or over, tested HIV negative, able to attend the clinic for regular three monthly review including for monitoring, sexual health care and support and to collect prescriptions, willing to stop NHS-funded PrEP if the eligibility criteria no longer apply and resident in Scotland. In addition at least one of the following should apply: current sexual partners, irrespective of gender, of people who are HIV positive and with a detectable viral load, MSM and transgender women with a documented bacterial rectal STI in the last 12 months, MSM and transgender women reporting condomless penetrative anal sex with two or more partners in the last 12 months and likely to do so again in the next three months or individuals, irrespective of gender, at an equivalent highest risk of HIV acquisition, as agreed with another specialist clinician.

Additional information: comparators

There are no active comparators.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
emtricitabine/tenofovir disoproxil	200mg/245mg, one tablet once daily	4,316

Costs from eVadis on 19 December 2016.

Additional information: budget impact

The submitting company estimated there would be 1,701 patients eligible for treatment with emtricitabine/ tenofovir disoproxil in all years. The estimated uptake rate was 58% in all years (986 patients).

The gross impact on the medicines budget was estimated to be £4.27m in all years. As no medicines were assumed to be displaced, the net medicines budget impact is equivalent to the gross impact. These figures assumed once daily dosing of emtricitabine/tenofovir disoproxil.

References

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19. Nandwani R, Valiotis G. PrEP in Scotland. October 2016.

This assessment is based on data submitted by the applicant company up to and including 17 February 2017.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These

contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.