SMC2718

cabotegravir prolonged-release suspension for injection and film-coated tablets (Apretude®)

ViiV Healthcare UK Ltd

10 January 2025

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

ADVICE: following a full submission

cabotegravir (Apretude®) is accepted for restricted use within NHSScotland.

Indication under review: Cabotegravir prolonged-release injection: in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg.

Cabotegravir tablets: in combination with safer sex practices for short term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg. Cabotegravir tablets may be used as:

- oral lead-in to assess tolerability of cabotegravir prior to administration of long acting cabotegravir injection.
- oral PrEP for individuals who will miss planned dosing with cabotegravir injection.

SMC restriction: Adults and adolescents (weighing at least 35kg) at high risk of sexually acquired HIV who are eligible for PrEP, including oral PrEP, but for whom oral PrEP is not appropriate to meet their HIV prevention needs.

Cabotegravir was superior to daily oral tenofovir disoproxil fumarate/emtricitabine in the reduction of incident HIV acquisitions in a phase IIb/III study in men who have sex with men and transgender women (HPTN 083) and in a phase III study in cisgender women (HPTN 084) at high risk of acquiring human immunodeficiency virus (HIV).

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Cabotegravir is an integrase strand transfer inhibitor (INSTI) which prevents human immunodeficiency virus (HIV) replication by binding to the HIV integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration within the host cell.[1, 2]

An oral lead-in dosing regimen may be used to assess tolerability to cabotegravir at a recommended dose of 30 mg once daily for approximately one month (at least 28 days). The recommended initial dose of cabotegravir injection is 600 mg via intramuscular (IM) injection. If an oral lead-in dosing regimen has been used, the first injection should be planned for the last day of oral lead-in or within 3 days thereafter. One month later, a second 600 mg IM initiation injection should be administered. After the second initiation injection, the recommended continuation injection dose in adults is a single 600 mg IM injection administered every 2 months.

Cabotegravir should be prescribed by a healthcare professional experienced in the management of HIV PrEP and each injection should be administered by a healthcare professional. See the Summary of Product Characteristics (SPC) for further information.[1, 2]

1.2. Disease background

Scotland hopes to end HIV transmission by 2030 and access to pre-exposure prophylaxis (PrEP) is a key component of primary prevention. Since July 2017 (when NHS funded PrEP first became available) and up until December 2023, PrEP has been accessed by 11,413 people in Scotland, mostly by gay, bisexual or other men who have sex with men (91%). The use of the service has continued to increase. The annual number of first ever HIV diagnoses has decreased from 226 in 2017 to 126 in 2023. Adherence to PrEP has a significant impact on efficacy and varies in different populations. Potential barriers that may lead to poor adherence include perceived risk, gender, HIV stigma, knowledge and engagement with sexual health services.[3-6]

1.3. Company proposed position

Adults and adolescents (weighing at least 35kg) at high risk of sexually acquired HIV who are eligible for PrEP, including oral PrEP, but for whom oral PrEP is not appropriate to meet their HIV prevention needs.

1.4. Treatment pathway and relevant comparators

Oral fixed-dose combination tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) PrEP is recommended to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk. Robust counselling on adherence to the PrEP dosing schedule is provided at initiation and maintenance consultations in combination with other protective measures including condom provision, behavioural support and advice on other sexually transmitted diseases. A HIV antigen/antibody test is recommended before starting PrEP and every 3 months while on treatment. Tenofovir alafenamide/emtricitabine (TAF/FTC) is an alternative option if TDF/FTC is unsuitable, often because of reduced renal function, increased fracture risk or severe lactose intolerance. However, its use should be discussed on a case-by-case basis with a local, regional or national multidisciplinary team and it is only licensed for at-risk men who have sex with men.[4, 6-8] If

oral PrEP is not appropriate, there are no alternative treatment options and standard of care with safe sex practices and condom provision would be offered. Clinical experts consulted by SMC considered that no PrEP and TDF/FTC were the most relevant comparators.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of cabotegravir for PrEP to reduce the risk of sexually acquired HIV-1 comes from HPTN 083 and HPTN 084. Details are summarised in Table 2.1.[9-11]

Table 2.1. Overview of relevant studies

Criteria	HPTN 083[9, 11]	HPTN 084[10, 11]
Study design	Multicentre, randomised, double-blind, phase IIb/III non-inferiority study.	Multicentre, randomised, double blind, phase III superiority study.
Eligible patients	• Men who have sex with men and transgender women aged ≥18 years. • Negative serologic HIV test at enrolment and undetectable HIV RNA viral load within 14 days of study entry. • High risk for sexually acquiring HIV based on at least one of the following (self-reported): ○ Condomless receptive anal intercourse 6 months prior to enrolment (monogamous HIV seronegative concordant relationship does not meet this criterion). ○ More than five partners 6 months prior to enrolment (regardless of condom use and HIV serostatus). ○ Stimulant drug use in the 6 months prior to enrolment. ○ Rectal or urethral gonorrhoea or chlamydia or incident syphilis 6 months prior to enrolment. ○ SexPro score of ≤16 (US sites only). • Creatinine clearance ≥60 mL/min.	• Born female and aged 18 to 45 years. • Negative HIV rapid antibody test or a laboratory-based antigen-antibody test, and undetectable HIV RNA up to 14 days before enrolment. • Sexually active with ≥2 episodes of vaginal intercourse within 30 days. • High risk of HIV infection based on a score ≥5 using a modified VOICE risk score. • Creatinine clearance ≥60 mL/min. • Negative pregnancy test and agreement to use of long-acting reversible contraception.
Treatments	**Blinded tablet lead-in phase:** • oral cabotegravir 30 mg once daily plus oral placebo or, • oral tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg once daily plus oral placebo, for up to 5 weeks. Participants with ≥50% pill adherence by pill count, and acceptable safety results were allowed to progress to the injection phase. **Blinded injection phase:** • cabotegravir 600 mg IM injection administered on week 5, week 9 and every 8 weeks thereafter plus daily oral placebo or, • oral tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg once daily plus IM placebo as per injection schedule above. **Unblinded one year[a]:** • Participants received their randomised study regimen without placebo. **Open-label extension**: • Patient choice between IM cabotegravir or oral tenofovir disoproxil fumarate/emtricitabine as per	

	regimens described above.
Randomisation	Participants were randomised equally to receive cabotegravir or tenofovir disoproxil fumarate/emtricitabine. Randomisation was stratified according to study site in both studies.
Primary outcome	The rate of incident HIV acquisitions. Calculated as the total number of participants with confirmed incident HIV infection during study follow-up of the blinded oral lead-in and injection phases divided by the person-years accumulated in each study group.
Other outcomes	• Adherence to study products. • Resistance mutations to study products.
Statistical analysis	Efficacy analyses were performed in the mITT population, which included all patients who underwent randomisation and were confirmed not to be living with HIV at study enrolment. Safety analyses were performed in all patients who had received at least one dose of study medicine.
[a]The studies were stopped early after review by the independent data safety monitoring board and participants entered a year 1 unblinded phase before protocols were amended and study sites transitioned to open-label extension studies.	

Abbreviations: HIV = Human Immunodeficiency Virus; IM = intramuscular; mITT = modified intention to treat; RNA = ribonucleic acid.

Study HPTN 083 was unblinded early in May 2020 as the non-inferiority threshold had been met and study HPTN 084 was unblinded early in November 2020 as prespecified superiority criteria had been met. The primary outcome results presented in Table 2.2 are for the blinded period of each study.

Table 2.2: Primary outcome results for HPTN 083 and HPTN 084 during the blinded study period in the mITT population[9-11]

	HPTN 083		HPTN 084	
	Cabotegravir (n=2,280)	**TDF/FTC (n=2,281)**	**Cabotegravir (n=1,614)**	**TDF/FTC (n=1,610)**
Median follow-up	1.4 years		1.2 years	
Number of HIV acquisitions	13	39	4	36
Incidence rate/100 PY	0.40	1.22	0.20	1.85
Bias-adjusted hazard ratio (95% CI)[a,b]	0.34 (0.18 to 0.62)		0.12 (0.05 to 0.31)	
Superiority p-value	<0.001		<0.001	
Non-inferiority p-value	<0.001		-	
CI = confidence interval, HIV = Human Immunodeficiency Virus, mITT = modified intention-to-treat, PY = person-years, TDF/FTC = tenofovir disoproxil fumarate/emtricitabine. [a]Adjusted to account for group-sequential study design and stopping early. [b]The upper bound of the CI in HPTN 083 was less than the non-inferiority threshold of 1.23. As the CI did not include 1 superiority could be tested and established if the point estimate was ≤0.74.				

Of the 13 HIV incident acquisitions in the cabotegravir group in HPTN 083, one was acquired prior to baseline, three were acquired during the oral lead-in period, five patients had no recent exposure to cabotegravir (no cabotegravir injections for at least 6 months prior to their first HIV-positive visit) and four occurred in participants with on-time injections. Of the four HIV acquisitions in the cabotegravir group in HPTN 084, two participants had no recent cabotegravir exposure and did not receive any injections, one participant was found to have HIV infection at enrolment following retrospective testing and one participant had delayed injection visits with the last injection given approximately 16 weeks before the first visit with confirmed HIV acquisition.[9-11]

In HPTN 083 and HPTN 084 respectively, there was 92% and 93% person-year coverage by cabotegravir injections during the blinded phase. After the oral lead-in, adherence to TDF/FTC was assessed in a randomly selected subset of participants. In HPTN 084, 42% of plasma samples yielded plasma tenofovir concentrations consistent with seven doses per week (≥40 nanogams/mL; for cisgender women daily use is required for optimum protection). Adherence to TDF/FTC reduced over time, with 72% and 18% of participants in each study having levels consistent with four doses per week (≥700 fmol/punch) measured over the past month.[9, 12 10]

HIV genotyping was performed at the first viraemic visit (HIV viral load >500 copies/mL) and any subsequent visit before the initiation of antiretroviral therapy. In HPTN 083, there were five cases of INSTI resistance identified during the blinded phase of the study. One was in a participant that had HIV infection at baseline and had received one cabotegravir injection, two participants acquired HIV during the oral lead-in and had resistance at the first viraemic visit, and two participants acquired HIV despite on-time injections and had resistance after receiving four cabotegravir injections. In the TDF/FTC group, resistance associated mutations were detected in 11 of the 42 (includes two positive baseline cases) HIV-positive cases during the blinded period of the study. This included seven cases of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance, three of NNRTI and nucleoside reverse transcriptase inhibitor (NRTI) and one case of NRTI resistance only.[13, 14] There were no major INSTI resistance mutations in the HIV acquisitions in the cabotegravir group during the blinded phase of HPTN 084. In the TDF/FTC group, one participant had a NRTI resistance mutation, nine had NNRTI resistance mutations and INSTI mutations were detected in 10 samples during the blinded phase.[15]

*Other data were also assessed but remain confidential.**

2.2. Health-related quality of life outcomes

In HPTN 083, patient-reported outcomes measuring tolerability and satisfaction were assessed using the Study Medication Satisfaction Questionnaire. Overall scores for both treatment groups were similar throughout the study and indicated a generally high degree of satisfaction with treatment; the scores in both groups were >60).[11, 16]

In HPTN 084, patient satisfaction with oral or injectable study medication was also assessed based on the inconvenience and pain or discomfort associated with receiving the medication. No pain or discomfort with the oral medication was reported by 56% in the cabotegravir group and 52% in the TDF/FTC group and for the injectable formulation by 43% and 52% in each group respectively.[11, 17, 18]

*Other data were also assessed but remain confidential.**

2.3. Supportive studies

HPTN 083 and HPTN 084 open-label extensions

In both HPTN 083 and HPTN 084, participants who completed the one-year unblinded phase could enter an ongoing open-label extension. Eligible participants could continue on their randomised PrEP regimen or crossover to the other regimen. In HPTN 084, 82% (2,472/3,028) entered the open-label extension study and most participants (78% [1,931/2,472]) chose to receive

cabotegravir. This included 67% (817/1,219) of participants that had initially been randomised to TDF/FTC. The most common reasons for choosing to receive cabotegravir in the open-label extension were: preference for injections (77%), desire for a convenient or discrete method (11%) and effectiveness (8%).[19]

HPTN 083 analysis was available for 803 participants from the US as they transferred over to the open-label extension before other regions. Most chose to receive cabotegravir (96% [770/803]) including 95% (368/388) of participants initially randomised to TDF/FTC. The most common reasons for choosing cabotegravir were: prefer injections/don't like pills (70%) and superior efficacy for HIV prevention (14%).[20]

HPTN 083-01 and HPTN 084-01 adolescent populations

HPTN 083-01 was an open-label single-arm study to evaluate the safety, tolerability and acceptability of cabotegravir for PrEP in sexually active adolescents assigned male at birth, aged ≤17 years in the US. The study recruited nine adolescents aged 15 to 17 years with a weight ≥35 kg. Although data were limited, cabotegravir concentrations at injection week 33 were similar to those observed in HPTN 083 (2.0 micrograms/mL versus 1.78 micrograms/mL). The safety tolerability and acceptability profile were similar to HPTN 083.[18, 21]

HPTN 084-01 was an open-label single-arm study to evaluate the safety of cabotegravir for PrEP in sexually active cisgender female adolescents, aged ≤17 years in Africa with a weight ≥35 kg. The study recruited 55 participants and concluded that cabotegravir was safe, acceptable and tolerable in this patient population. Age did not appear to affect cabotegravir pharmacokinetics although some issues were identified regarding the impact of lower weight on exposure.[18, 22]

No patients in HPTN 083-01 or HPTN 084-01 acquired HIV.[18]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing cabotegravir with no PrEP, the submitting company conducted an indirect treatment comparison (ITC) as detailed in Table 2.3. This has been used to inform the economic case.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian hierarchical meta-regression (to account for variation in adherence). This analysis was also used to estimate the relationship between adherence and efficacy.
Population	Cisgender women, men who have sex with men and transgender women aged 18 years and older who are at an increased risk of acquiring human immunodeficiency virus type 1 (HIV-1) infection.
Comparators	No pre-exposure prophylaxis (PrEP) and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC).
Studies included	10 studies.
Outcomes	Reduction in risk of HIV acquisition.
Results	The indirect comparison results suggest that cabotegravir has superior efficacy compared with no PrEP in reducing the risk of HIV acquisition: the relative estimated effectiveness was 91% (97.5% credible interval [Crl]: 83% to 96%) in men who have sex with men and transgender women (HPTN 083 population), and 92% (97.5% Crl: 83% to 97%) in cisgender women (HPTN 084 population).[23]

3. Summary of Safety Evidence

In HPTN 083 during the blinded study period at data cut-off 14 May 2020, the median exposure was 457 days (range: 1 to 1,093 days) in the cabotegravir group and 471 days (range: 1 to 1,131 days) in the TDF/FTC group. In each group respectively, patients reporting a grade 3 or higher adverse event (AE) were 33% versus 33%, serious AE were 4.8% versus 4.6% and the proportion of AEs that led to discontinuing therapy was 5.9% versus 4.0%.[9, 11]

In HPTN 084 during the blinded study period at data cut-off 5 November 2020, the median exposure was 453 days in both groups (range: 1 to 1,072 days for cabotegravir and 1 to 1,018 days for TDF/FTC). In each group respectively, patients reporting a grade 3 or higher AE were 16% versus 17%, serious AE were 1.5% versus 2.0% and the proportion of AEs that led to discontinuing therapy was 1.1% versus 1.4%.[10, 11]

The most common treatment-emergent AEs, with the exception of injection site reactions (ISRs), were similar between groups. Injection site pain occurred in 75% versus 30% of patients in the cabotegravir and TDF/FTC groups respectively in HPTN 083 and 32% versus 9.1% of patients in HPTN 084. [11]

ISRs considered to be treatment-related were reported in a higher proportion of patients in the cabotegravir group compared with the TDF/FTC group in both studies (HPTN 083: 81% versus 31%; HPTN 084: 38% versus 11%); these were grade 3 in 2.4% in HPTN 083 and 0.1% in HPTN 084 (no participants experienced grade 4 or 5 reactions). In HPTN 083 and HPTN 084 respectively, 2.1% and 0% of participants in the cabotegravir group discontinued treatment because of an ISR. Injection site pain was the most frequently reported ISR in the cabotegravir group in both studies (HPTN 083: 81%; HPTN 084: 34%); injection site nodule, induration and swelling were also commonly reported. In general, reactions decreased in severity and frequency over time.[1, 11]

Overall, regulatory authorities concluded that cabotegravir was well-tolerated with a safety profile similar to that of TDF/FTC, with the exception of ISRs.

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In HTPN 083 and HPTN 084, cabotegravir oral lead-in followed by long-acting injections demonstrated superiority to daily oral TDF/FTC for reducing the risk of HIV-1 acquisition. In the primary analysis of the blinded phase this was associated with a 66% relative risk reduction in men who have sex with men and transgender women and an 88% relative risk reduction in cisgender women. The treatment effect was consistent across prespecified subgroups in both studies.
- HPTN 083 and HPTN 084 were at low risk of bias as they had a double-blind and double-dummy study design, and HIV-1 acquisitions were confirmed centrally.

4.2. Key uncertainties

- The submitting company has requested that SMC consider cabotegravir for use in a subpopulation of people who are eligible for PrEP, including oral PrEP, but for whom oral PrEP is not appropriate to meet their HIV prevention needs. The studies' eligibility criteria do not align directly with this proposed positioning population as people unable to take oral PrEP were excluded from HPTN 083 and HPTN 084. There is limited evidence in people with suboptimal adherence: 14% in HPTN 083 and 44% of patients randomised to TDF/FTC in HPTN 084 had undetectable tenofovir levels (<0.31 nanograms/mL) however, no subgroup analysis of these participants or of other cohorts with poor adherence was presented. It is uncertain if there are any significant effect-modifying differences between these populations. The proposed positioning also excludes those who are adherent to oral PrEP from having the choice to switch to cabotegravir.[9, 10]

- There is no direct evidence comparing cabotegravir with no PrEP, which is a relevant comparator based on the proposed positioning. The submitting company performed an indirect comparison using Bayesian hierarchical meta-regression analyses which were associated with a number of limitations:

    - The target population did not align with the proposed positioning, as all studies included people taking oral PrEP. Furthermore, adolescents were not included in the studies and there were limited data in older adults. Therefore, the results may not be generalisable to these groups.

    - There were considerable differences between studies in terms of methodology, inclusion criteria, population demographics and characteristics, location of study sites and interventions. Meta-regression was used to account for variation in TDF/FTC adherence, which was strongly related to efficacy. However, there were insufficient studies to adjust for other characteristics (such as study location), which increases uncertainty. Alternative methods that account for differences between studies may have been appropriate.

    - Some studies were stopped early because of high dropout rates, logistical challenges or lack of efficacy, which may have underpowered the results and increase risk of potential bias.

    - Safety outcomes and patient-reported outcomes were not assessed.

Although the overall results of the ITC seem reasonable that cabotegravir is more effective than no PrEP in reducing the risk of HIV acquisition, there is uncertainty regarding the point estimates.

- Adherence to PrEP is an important factor when evaluating efficacy and preventing potential drug resistance. It is uncertain if the high injection adherence rates, and thus relative efficacy to TDF/FTC, observed in HPTN 083 and HPTN 084 studies would be transferable to Scottish clinical practice and in the subpopulation of people included within the positioning.

- In HPTN 083 and HPTN 084, TDF/FTC was taken as a regular daily dose, however event-based dosing (off-label) is an option for people who do not have hepatitis B, typically have sex less than once a week and know when they are likely to have sex.[24] A Scottish expert indicated that approximately 27% of patients in a local health board use event-based dosing. There is no evidence comparing cabotegravir with this on-demand oral dosing regimen. There is also no comparative evidence for cabotegravir with TAF/FTC however, an SMC clinical expert indicated that this formulation is prescribed for less than 5% of oral PrEP users.

- There are some limitations of the studies, which could potentially affect the generalisability of results to a Scottish population. Participants aged ≥50 years accounted for only 2.7% of the study population in HPTN 083 and there were no participants recruited to HPTN 084 aged >45 years. Although most people prescribed PrEP in Scottish clinical practice are <40 years of age, there is a small proportion that receive treatment who are >50 years (11% between July 2017 and December 2023). The efficacy data in adolescents is limited and mainly based on pharmacokinetic extrapolations because of the low number of participants recruited to HPTN 083-01 and HPTN 084-01. There were no UK or European study sites in HPTN 083, and HPTN 084 was conducted in Africa only. It is uncertain if adherence, level of HIV risk in the treated population, and sexual behavioural patterns would be reflective of people who would access PrEP in Scotland.[5, 9, 10]

4.3. Clinical expert input

Clinical experts consulted by SMC considered the introduction of cabotegravir for the subpopulation of patients whose PrEP need is not met by oral PrEP fills an unmet need and is a therapeutic advancement because it will provide a prevention option with an alternative route of administration for those unable to use or whose use of oral options is suboptimal. They indicated that its place in therapy would be for use in high-risk patients that could not safely take daily oral or event-based doses of oral PrEP because of medical, demographic or social reasons.

4.4. Service implications

An increase in clinic allocation and clinical staff resource will be required to adequately counsel patients, conduct monitoring and administer injections bimonthly. More frequent HIV testing and additional HIV-RNA testing compared with oral PrEP could impact laboratory resource. Patients will also have to attend clinic visits bimonthly, which may be inconvenient and are more frequent than if using oral PrEP (3 to 6 monthly).

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information.

5. Summary of Patient and Carer Involvement

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

- We received patient group submissions from Waverley Care and the National Aids Trust, both organisations are registered charities.

- Waverley Care has received 3% pharmaceutical company funding in the past two years, including from the submitting company. The National Aids Trust has received 13% pharmaceutical company funding in the past two years, including from the submitting company.
- People in Scotland who are at high risk of contracting HIV can face complex, daily challenges that affect both their mental well-being and social lives. HIV-related stigma remains a serious issue, influencing self-esteem and social interactions, especially among underserved communities including men who have sex with men, transgender individuals, and Black African communities. These groups already face societal discrimination, and the additional layer of HIV stigma can lead to isolation, fear of judgement, and reluctance to access preventive care.
- The current daily oral PrEP has adherence challenges, especially for those experiencing intimate partner violence, housing instability, or substance use issues. Long-acting cabotegravir PrEP provides another option for people to prevent HIV. Long-acting PrEP has the potential to increase adherence and bring new communities into PrEP access.
- Cabotegravir is an effective and much-needed alternative for individuals who struggle with accessing or adhering to daily oral PrEP.
- For underserved communities, the availability of a long-acting injectable like cabotegravir might substantially improve uptake and adherence, helping to close existing gaps in HIV prevention.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (72 years)
Population	Adults and adolescents (weighing at least 35kg) at high risk of sexually acquired HIV who are eligible for PrEP, including oral PrEP, but for whom oral PrEP is not appropriate to meet their HIV prevention needs.
Comparators	Oral tenofovir disoproxil fumarate with emtricitabine (TDF/FTC) or no PrEP.
Model description	The model compared three treatment arms, cabotegravir, TDF/FTC and no PrEP. The company utilised a Markov state-transition model with 5 discrete health states: treatment with cabotegravir, treatment with TDF/FTC, no PrEP, living with HIV and an all-absorbing dead state. Patients in each arm of the model started in their respective treatment health states. Patients in the cabotegravir arm could discontinue treatment and transition to the TDF/FTC or no PrEP health states. Patients in the TDF/FTC arm could not be treated with cabotegravir so could only discontinue to no PrEP. Patients who discontinued PrEP (cabotegravir or TDF/FTC) could not recommence treatment. Patients in the cabotegravir, TDF/FTC and no PrEP health states had a chance each cycle to transition to the living with HIV health state.

Clinical data	Clinical data for the efficacy of cabotegravir compared to TDF/FTC, rates of adverse events and adherence to TDF/FTC were from the HPTN 083 and HPTN 084 studies. The proportion of cisgender women, men who have sex with men and transgender women was estimated based on Scottish data capturing sex, gender and sexual orientation of people prescribed PrEP. The starting age in the model was estimated using the median age of people prescribed PrEP in Scotland. The baseline risk of HIV acquisition with no PrEP was from a registry study for men who have sex with men and transgender women, and from the company's ITC for the cisgender women population. This resulted in a weighted mean rate of HIV acquisition with no PrEP of 4.89 per 100 person years (PY). Transition probabilities from the cabotegravir use and TDF/FTC use health states were according to the respective effectiveness for reduction in relative risk of HIV acquisition compared to no PrEP from the company's ITC. Each HIV acquisition in the model was associated with onward transmissions based dynamic models of HIV transmissions. General population mortality was applied for people not living with HIV. Mortality for people living with HIV was general population mortality adjusted by a standardised mortality ratio for HIV treated with antiretroviral therapy (ART) from the literature.
Extrapolation	Relative effectiveness of cabotegravir and TDF/FTC compared to no PrEP for the reduction of HIV acquisition was constant over the first 5-years of the model, which was considered the total lifetime elevated risk period for HIV acquisition. This was based on observed discontinuations from PrEP from real world evidence. Patients who discontinued PrEP did not maintain any residual benefit for reducing risk of HIV acquisition. At the end of the 5-year at-risk period all remaining patients receiving PrEP discontinued treatment and patients not living with HIV were no longer at risk of HIV acquisition.
Quality of life	Patients not living with HIV assumed age and sex adjusted general population quality of life. A utility decrement from the literature (-0.11) was applied per cycle for people living with HIV. No utility decrements were included for adverse events.
Costs and resource use	Costs were included for medicine acquisition and administration, sexual health clinic visits, monitoring tests, management of adverse events, ART for treating resistant and non-resistant HIV and health care resource use for managing HIV.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The base case versus both no PrEP and TDF/FTC showed cabotegravir was dominant compared to the comparator meaning it was estimated as resulting in lower costs and better health outcomes for patients using the PAS price**.**

6.3. Sensitivity analyses

Table 6.3a Selected scenario analysis results versus no PrEP (PAS price)

	Scenario	Base case parameter	Value in scenario analysis	ICER versus no PrEP
1	Persistence for cabotegravir compared with TDF/FTC	Increased persistence of 20%	35%	Dominant
2			0%	Dominant
3	At-risk period	5 years	3 years	Dominant
4			10 years	Dominant
5	Baseline risk of HIV acquisition with no PrEP	4.9 per 100 PY	0.3 per 100 PY	146,179
6			0.63 per 100 PY	29,992
7			0.87 per 100 PY	Dominant
8			3 per 100 PY	Dominant
9	Subsequent HIV transmissions	Men who have sex with men / transgender women 1.38, cisgender women 0.80	men who have sex with men / transgender women 0.7, cisgender women 0.4	Dominant
10	Utility decrement for living with HIV	-0.11	-0.05	Dominant

Abbreviations: HIV = human immunodeficiency virus; ICER = incremental cost-effectiveness ratio; incr. = incremental; LYG = life-year gain; PrEP = pre-exposure prophylaxis; PY = person year; TDF/FTC = tenofovir disoproxil fumarate with emtricitabine; QALY = quality-adjusted life year

Table 6.3b Selected scenario analysis results versus TDF/FTC (PAS price)

#	Scenario	Base case parameter	Value in scenario analysis	ICER versus TDF/FTC
1	Persistence for cabotegravir compared with TDF/FTC	Increased persistence of 20%	35%	Dominant
2			0%	Dominant
3	At-risk period	5 years	3 years	Dominant
4			10 years	Dominant
5	Baseline risk of HIV acquisition with no PrEP	4.9 per 100 PY	0.3 per 100 PY	406,961
6			0.63 per 100 PY	166,538
7			0.87 per 100 PY	101,072
8			3 per 100 PY	Dominant
9	Proportion discontinuing cabotegravir to TDF/FTC	Base case value commercial in confidence	0%	Dominant
10	Subsequent HIV transmissions	men who have sex with men / transgender	men who have sex with men /	Dominant

		women 1.38, cisgender women 0.80	transgender women 0.7, cisgender women 0.4	
11	Utility decrement for living with HIV	-0.11	-0.05	Dominant

Abbreviations: HIV = human immunodeficiency virus; ICER = incremental cost-effectiveness ratio; incr. = incremental; LYG = life-year gain; PrEP = pre-exposure prophylaxis; PY = person year; TDF/FTC = tenofovir disoproxil fumarate with emtricitabine; QALY = quality-adjusted life year

6.4. Key strengths

- Availability of randomised evidence from the HPTN 083 and HPTN 084 studies that reported that cabotegravir reduced HIV acquisition compared to a relevant comparator that seemed most likely to be displaced in Scottish clinical practice according to clinical experts consulted by SMC.
- The comparators included were appropriate and experts consulted by SMC considered that they reflected Scottish clinical practice.

6.5. Key uncertainties

- There was a lack of direct evidence comparing cabotegravir to no PrEP to inform model parameters in the economic evaluation. Therefore, the estimate of relative efficacy of cabotegravir versus no PrEP used in the economic evaluation was informed by the ITC.
- A key issue was that the baseline risk of HIV acquisition without PrEP in the model was uncertain as it was from a population that clinical experts consulted by SMC considered were higher risk than the population eligible for PrEP in Scottish clinical practice. These clinical experts cited a retrospective cohort study that evaluated new HIV acquisitions in men who have sex with men who attended sexual health clinics in Scotland before and after the introduction of a PrEP programme. This study reported rates of HIV acquisition in this population of 0.5 per 100 PY before the introduction of a PrEP programme which fell to 0.3 per 100 PY for people not taking PrEP post-implementation. In a scenario that used the rate from the literature cited by Scottish clinical experts for the baseline rate of HIV acquisition without PrEP, this resulted in a much higher estimate of cost effectiveness (Scenario 5). The true rate in the population remains unknown but it was helpful to the Committee to see this explored in sensitivity analyses scenarios 5-8 in tables 6.3a and 6.3b.
- Onwards transmissions of HIV in Scottish clinical practice are highly uncertain due to a paucity of evidence. The evidence used in the company's economic evaluation was from studies that modelled HIV transmissions in populations with zero PrEP use compared to the introduction of PrEP. Cabotegravir would be introduced in a population where a significant proportion of people will be suitable for oral PrEP. Therefore, it seemed likely that the transmission rates from these studies were likely to overestimate onward transmissions in the model compared with Scottish clinical practice. A scenario where these rates were halved resulted in higher estimates of cost effectiveness (Scenario 9 table 6.3a and scenario 10 table 6.3b).

- Utility decrements for people living with HIV were uncertain. The utility decrement applied in the model may overestimate the impact of HIV on health-related quality of life in patients with recently acquired HIV, even when controlled for factors such as age and disease severity. When an alternative utility decrement was used this resulted in lower incremental QALY gains (Scenario 10 table 6.3a and scenario 11 table 6.3b).
- Persistence was defined as the percentage of people remaining on PrEP over time and determined the discontinuation rates in the economic model. Persistence to cabotegravir was uncertain as this was not directly assessed in the pivotal studies. Persistence was assumed to be higher for cabotegravir compared to TDF/FTC, but clinical experts consulted by SMC thought this was uncertain. A scenario that assumed equal persistence to cabotegravir resulted in a higher estimate of cost-effectiveness (Scenario 2).
- Subsequent treatment following cabotegravir was uncertain. The company assumed that some patients would commence TDF/FTC following treatment with cabotegravir, however this seemed uncertain and may contradict the proposed positioning. There was no evidence for effectiveness of TDF/FTC in a population that discontinued cabotegravir. A scenario where all patients who discontinued cabotegravir received no PrEP resulted in a higher estimate of cost-effectiveness (Scenario 9 table 6.3b).
- Evidence for the at-risk period applied in the model was from evidence of mean treatment duration from a single prescription episode. Clinical experts consulted by SMC stated that people may frequently stop and restart PrEP. There is no evidence for the duration of time that individuals are at elevated risk of HIV cumulatively over their lifetime and are eligible for PrEP in Scottish clinical practice. A shorter at-risk period constrains the period that people can be on the relatively more expensive cabotegravir versus TDF/FTC. A scenario where the at-risk period was 10-years resulted in a higher estimate of cost-effectiveness (Scenario 4).

*Other data were also assessed but remain confidential.**

7. Conclusion

After considering all the available evidence the Committee accepted cabotegravir for restricted use in NHSScotland.

8. Guidelines and Protocols

The Scottish Health Protection Network (SHPN) published "Guidance on HIV Prevention in Men who have Sex with Men (MSM)" in 2019.[25]

The British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH) published "BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP)" in 2018.[4]

9. Additional Information

9.1. Product availability date

6 December 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Oral lead-in and oral bridging **Cabotegravir tablets** **Injections** **Cabotegravir injections**	**30 mg taken orally once daily** **600 mg given intramuscularly one month apart for the first 2 months and then every 2 months thereafter.**	**Year 1 with oral lead-in** **7,821** **Year 1 without oral lead-in** **8,379** **Year 2 onwards** **7,182**

Costs from the company submission.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 15 November 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.