Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2376

cabotegravir 600mg prolonged-release suspension for injection (Vocabria®)

ViiV Healthcare

10 September 2021

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 (Vocabria®) is accepted for use within NHSScotland.

Indication under review: in combination with rilpivirine prolonged-release injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class

Cabotegravir 600mg prolonged release injection plus rilpivirine 900mg prolonged-release injection every 2-months was non-inferior to cabotegravir 400mg plus rilpivirine 600mg every month in terms of the proportion of patients losing virological suppression in a phase III study. Cabotegravir 400mg prolonged release injection plus rilpivirine 600mg prolonged-release injection was non-inferior to oral antiretroviral therapy.

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.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class.

Dosing Information

Oral lead-in

Prior to the initiation of cabotegravir and rilpivirine injections, oral cabotegravir together with oral rilpivirine should be taken for approximately one month (at least 28 days) to assess tolerability to cabotegravir and rilpivirine. One cabotegravir 30mg tablet should be taken with one rilpivirine 25mg tablet, once daily. When administered with rilpivirine, cabotegravir tablets should be taken with a meal (see cabotegravir tablet prescribing information).

Every 2 Month Dosing

On the final day of oral lead-in therapy, the recommended initial cabotegravir injection is a single 600mg intramuscular injection, and the recommended initial rilpivirine injection is a single 900mg intramuscular injection (month 2). One month later (month 3), a second cabotegravir 600mg intramuscular injection and rilpivirine 900mg intramuscular injection should be administered. Patients may be given the second injections up to 7 days before or after the scheduled dosing date. After the initiation injections, the recommended cabotegravir and rilpivirine continuation injection doses in adults is a single 600mg cabotegravir intramuscular injection and a single 900mg rilpivirine intramuscular injection (month 5) administered every 2 months. Patients may be given injections up to 7 days before or after the date of the every 2 month injection schedule.

Prior to starting cabotegravir and rilpivirine injection, healthcare professionals should have carefully selected patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses.

Following discontinuation of cabotegravir and rilpivirine injection, it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the final injection of cabotegravir when dosed monthly and no later than two months after the final injection of cabotegravir when dosed every 2 months

Cabotegravir and rilprivirine should be prescribed by physicians experienced in the management of HIV infection. Each injection should be administered by a healthcare professional. [12]

Product availability date

13 September 2021

Summary of evidence on comparative efficacy

Cabotegravir is a new integrase strand transfer inhibitor (INSTI) that blocks the strand transfer step of retroviral DNA integration, which is essential for the HIV replication cycle. It is similar in structure to dolutegravir and has been formulated as a prolonged release suspension for injection. It is given concomitantly but by separate injection with a prolonged release injection of rilpivirine to form a combined long-acting regimen for the treatment of HIV-1.[1-3] The SPCs state that, after an oral lead-in, cabotegravir can be administered as 400mg every month or as 600mg every 2 months and rilpivirine as 600mg every month or 900mg every 2 months.[1, 2] However the submitting company has advised that only cabotegravir 600mg and rilpivirine 900mg for administration every 2 months will be marketed and available within the UK.

The key evidence to support the 2-monthly administration of cabotegravir plus rilpivirine injections comes from ATLAS-2M versus monthly injections but this is indirectly reliant on evidence of non-inferiority of cabotegravir plus rilpivirine prolonged release injections versus oral antiretroviral therapy (ART) from the FLAIR and ATLAS studies. Therefore, both these studies are also discussed below.

ATLAS-2M is an ongoing, randomised, open-label, phase IIIb non-inferiority study which evaluated the efficacy and safety of cabotegravir plus rilpivirine administered every 2 months (n=522) versus every month (n=523). It was performed in patients with HIV-1 who were virologically suppressed following treatment with stable oral ART for ≥6 months; the majority of study patients were enrolled directly from the ATLAS study and additional patients enrolled had received standard of care. The FLAIR and ATLAS studies were similarly designed multicentre, randomised, open-label, phase III non-inferiority studies which compared cabotegravir plus rilpivirine administered intramuscularly every month with oral ART. The FLAIR study was performed in treatment-naïve patients with HIV-1 who achieved viral suppression in response to 20 weeks of oral induction therapy with dolutegravir / abacavir / lamivudine. It compared cabotegravir plus rilpivirine intramuscularly every month (n=283) with continued treatment with dolutegravir / abacavir / lamivudine (n=283). The ATLAS study was performed in patients with HIV-1 who had HIV-1 RNA levels <50 copies/mL for ≥6months while on standard oral ART and compared cabotegravir plus rilpivirine intramuscularly every month (n=308) with continued treatment with previous oral ART (n=308).[4-6]

Long-acting therapy comprised an oral therapy lead-in of cabotegravir 30mg and rilpivirine 25mg daily for 4 weeks to assess tolerability (except for patients in ATLAS-2M who had already received cabotegravir and rilpivirine injections). At week 4 of FLAIR and ATLAS, patients received a loading dose each of 600mg of cabotegravir and 900mg of rilpivirine intramuscularly in the gluteus muscle. Second and third injections of cabotegravir 400mg and rilpivirine 600mg were administered 21 and 28 days after the loading dose and subsequent injections 21 to 35 days thereafter. In ATLAS-

2M, patients were randomised equally to receive cabotegravir 600mg and rilpivirine 900mg intramuscularly every 8 weeks or cabotegravir 400mg and rilpivirine 600mg intramuscularly every 4 weeks. Patients who had not received previous cabotegravir and rilpivirine followed the oral lead-in and loading doses for FLAIR and ATLAS. In ATLAS-2M, randomisation was stratified according to previous oral or intramuscular exposure to cabotegravir and rilpivirine (0 weeks, 1 to 24 weeks and >24 weeks); in FLAIR, according to the patient's HIV-1 RNA level at baseline before induction therapy (<100,000 or ≥100,000 copies/mL) and by sex at birth and in ATLAS according to the class of medicine in the baseline ART (protease inhibitor, INSTI or NNRTI).[3, 4]

In all three studies, the primary outcome was the percentage of patients who had a plasma HIV-1 RNA level ≥50 copies/mL at week 48 of the maintenance period with analyses performed using FDA snapshot algorithm in the intention-to-treat exposed (ITT-E) population (all randomised patients who received at least one dose of study medication during the maintenance period of the studies). In ATLAS-2M, since the upper boundary of the 95% confidence interval (CI) for the between group difference at week 48 was less than the pre-specified non-inferiority margin of 4%, the 2-monthly dosing was non-inferior to monthly dosing. In FLAIR and ATLAS, the upper boundary of the 95% CI for the difference at week 48 was less than the pre-specified non-inferiority margin of 6% and cabotegravir plus rilpivirine was considered non-inferior to oral ART. The studies were also powered to test for non-inferiority in the key secondary outcome, the percentage of patients who had a plasma HIV-1 RNA level <50 copies/mL at week 48. Using the same pre-defined margins, non-inferiority over comparator group was demonstrated in all three studies. Details are presented in table 1.[3-5]

Table 1: results for the primary and key secondary outcomes in the ITT-E population of the all studies based on FDA snapshot analysis[1, 3-5]

ATLAS-2M	**Cabotegravir + rilpivirine every month**	**Cabotegravir + rilpivirine every 2-months**	**Difference (95% CI)**
HIV-1 RNA ≥50 copies/mL at week 48	1.7% (9/522)	1.0% (5/523)	0.8% (-0.6 to 2.2)
HIV-1 RNA <50 copies/mL at week 48	94% (492/522)	93% (489/523)	0.8% (-2.1 to 3.7)
FLAIR	**Cabotegravir + rilpivirine every month**	**Oral ART**	**Difference (95% CI)**
HIV-1 RNA ≥50 copies/mL at week 48	2.1% (6/283)	2.5% (7/283)	-0.4% (-2.8 to 2.1)
HIV-1 RNA <50 copies/mL at week 48	94% (265/283)	93% (264/283)	0.4% (-3.7 to 4.4)

ATLAS	Cabotegravir + rilpivirine every month	Oral ART	Difference (95% CI)
HIV-1 RNA ≥50 copies/mL at week 48	1.6% (5/308)	1.0% (3/308)	0.6% (-1.2 to 2.4)
HIV-1 RNA <50 copies/mL at week 48	93% (285/308)	96% (294/308)	-2.9% (-6.7 to 0.8)

CI= confidence intervals; mL= millilitre

Confirmed virologic failure at week 48 (defined as two consecutive plasma HIV-1 RNA levels ≥200 copies/mL after prior suppression to <200 copies/mL) was another secondary outcome and was experienced by 1.5% (8/522) and 0.4% (2/523) of patients in the 2-monthly and monthly groups of ATLAS-2M respectively; and in 1.4% (4/283) and 1.1% (3/283) of the cabotegravir plus rilpivirine and oral ART groups of FLAIR and in 1.0% (3/308) and 1.3% (4/308) respectively in ATLAS.[3-6]

Patient satisfaction scores were found to be numerically higher with cabotegravir plus rilpivirine compared with oral ART in FLAIR and ATLAS and >90% of responding patients preferred injections over oral therapy. In ATLAS-2M, more patients preferred 2-monthly injections than monthly injections over oral ART.[3-6]

The company presented an adjusted indirect treatment comparison (ITC) of cabotegravir plus rilpivirine every 2-months with oral ART using Bucher methods. This used results from a subgroup of ATLAS-2M who had not previously received cabotegravir and rilpivirine injections (n=654) and the pooled analysis of FLAIR and ATLAS (n=1,182) using cabotegravir and rilpivirine monthly injections as a common control group. The ITC assessed a number of outcomes: HIV-1 RNA <50 copies/mL at week 48; HIV-1 RNA ≥50 copies/mL at week 48; CD4+ cell change from baseline, no virologic data at week 48; discontinuations due to AEs at week 48 and grade 3 to 5 AEs (excluding injection site reactions). The results suggest that there was no evidence of a difference between cabotegravir plus rilpivirine every 2-months with oral ART for any of the outcomes.

Summary of evidence on comparative safety

In the ATLAS-2M study, any treatment-emergent adverse event (AE) was reported by 91% (473/522) of patients in the cabotegravir and rilpivirine every 2-months group and 92% (482/523) in the cabotegravir and rilpivirine every month group and these were serious in 5.2% versus 3.6% and led to discontinuation therapy in 2.3% versus 2.5%. The most frequently reported treatment-emergent AEs in the respective groups were: injection site pain (71% versus 69%), nasopharyngitis (14% versus 14%), injection site nodule (10% versus 17%), upper respiratory tract infection (9.6% versus 14%), injection site induration (7.9% versus 7.5%), injection site discomfort (6.9% versus 7.8%), headache (6.7% versus 6.9%), diarrhoea (6.3% versus 7.1%), swelling (6.1% versus 5.2%) and pruritus (5.2% versus 4.8%).[6]

In a pooled safety analysis of FLAIR and ATLAS, any treatment-emergent AE was reported by 95% (561/591) of patients in the cabotegravir plus rilpivirine group and 75% (444/591) in the oral ART group and these were considered treatment-related in 83% and 5.9% of patients respectively. A

serious AE was reported in 4.1% and 4.2% respectively and 3.7% and 1.5% respectively discontinued therapy due to an AE. The most frequently reported treatment emergent AEs in the respective groups were: injection site pain (79% versus NA); nasopharyngitis (18% versus 15%); upper respiratory tract infection (11% versus 8.8%); headache (12% versus 6.4%); diarrhoea (8.8% versus 6.4%); injection site nodule (14% versus NA) and injection site induration (12% versus NA).[7]

Summary of clinical effectiveness issues

HIV-1 infection results in chronic activation of the immune system and a subsequent gradual loss of CD4+ T cells eventually leading to a state of acquired immunodeficiency (AIDS). One of the predictors for HIV-1 disease progression is the viral load, plasma HIV-1 RNA. The BHIVA guideline recommends that the primary aim of ART is to prevent the mortality and morbidity associated with chronic HIV by suppressing, and subsequently maintaining, the HIV-1 viral load to levels that are at least below the limit of detection of most commonly used assays (50 copies/ml of blood) and therefore the preserving the immune system. This also reduces transmission.

Current standard of care for the treatment of HIV-1 infection uses combination of ART to suppress viral replication to below detectable limits, allow CD4 cell counts to increase, and stop disease progression. In treatment-naive patients, current guidelines recommend initial therapy consists of a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) and a third agent from either ritonavir-boosted protease inhibitor, non- nucleoside reverse transcriptase inhibitors (NNRTI) or integrase inhibitor (INI). The current preferred NRTIs are tenofovir disoproxil plus emtricitabine or tenofovir alafenamide plus emtricitabine. Preferred third agents are ritonavir boosted atazanavir; ritonavir boosted darunavir; dolutegravir; cobicistat boosted elvitegravir; raltegravir or rilpivirine.[3, 8] There are a number of single tablet combination products available which aim to improve adherence to combination regimens and dual therapy regimens are also available, for example dolutegravir / rilpivirine (Juluca®) and dolutegravir / lamivudine (Dovato®). Cabotegravir is the first long-acting injectable ART regimen to become available in the UK. When used in combination with rilpivirine prolonged release injection, this removes the need for daily oral treatment which may improve adherence to treatment in some patients.

The company has advised that only cabotegravir 600mg and rilpivirine 900mg prolonged release injections for 2-monthly administration will be marketed and available in the UK. The evidence to support the 2-monthly administration of cabotegravir and rilpivirine comes from one study only, ATLAS-2M, which confirmed the non-inferiority of 2-monthly and monthly administration. Cabotegravir and rilpivirine every 2-months was associated with a numerically higher rate of patients with HIV-1 RNA ≥50 copies/ml at week 48 (1.7% versus 1.0%, respectively) and confirmed virologic failure (1.5% and 0.4%). However, the differences were not statistically significant, with results well within the predefined margins for non-inferiority, and it was concluded that both regimens had comparable efficacy.[3, 6]

It was noted that certain subgroups of patients in the 2-monthly dosing group were at more risk of virologic failure and should be considered to start on monthly dosing to minimise this risk. A post hoc multivariate analyses of all three studies found that at least two of the following baseline

factors were risks for virologic failure: rilpivirine resistance mutations identified by proviral resistance testing, HIV-1 subtype A6/A1, or BMI >30mg/m^2. The SPC advises caution in patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI ≥30 kg/m^2 or HIV-1 A6/A1 subtype. Availability of only cabotegravir 600mg for 2-monthly dosing would not allow these patients to start on 400mg monthly dosing and would remove the flexibility in dosing for patients and the service. [1, 3]

The patient populations of ATLAS-2M, FLAIR and ATLAS are generally asymptomatic, white patients without immunologic deficiency. The studies attempted to recruit a significant proportion of women (25-30%) and 22%, 33% and 28% were female. These factors may affect the generalisability of study results to all HIV-1 patients in clinical practice.

The study primary outcomes were assessed 48 weeks after starting long-acting injections and longer term data are required to confirm the efficacy and safety of this potentially life-long treatment.

Study patients received oral lead-in therapy with one month of cabotegravir and rilpivirine tablets to ensure tolerability before starting prolonged release injections. This is in line with the recommended dosing for cabotegravir and rilpivirine. The SPCs also recommends that oral therapy may be used as bridging in case of missed injection. However during the main studies, there are limited data to support this, with only eight missed injections and oral bridging used.[1-3]

There is no direct evidence comparing cabotegravir plus rilpivirine every 2-months with oral ART. The results of the ITC suggest that there is no evidence of a difference between treatments for the range of outcomes assessed. There are a number of limitations in the ITC including use of only a subgroup of patients from the ATLAS-2M study, who had not received previous cabotegravir and rilpivirine, to balance the use of previous treatments; ATLAS-2M was not powered for this subgroup analysis. In addition, there were differences between the FLAIR and ATLAS studies in oral ART used. Subgroup analysis of the ITC stratified by baseline third active medicine class found results were consistent with the overall ITC results but the wider confidence intervals suggested greater uncertainty. The oral ART used in FLAIR (dolutegravir, abacavir and lamivudine or dolutegravir plus two other NRTIs) and ATLAS (two NRTIs plus an INSTI, NNRTI or protease inhibitor) may not represent the range of oral ART used in clinical practice and may limit the generalisability of the ITC results to patients. There are a number of single tablet formulations of oral ART regimens available, which aid compliance with treatment.

The introduction of cabotegravir prolonged release injection for use in combination with rilpivirine prolonged release injection would offer the first long-acting injectable ART. For selected patients this may aid adherence to treatment and reduce virologic failure, resistance and disease progression. However, patients eligible for switching to this treatment are required to be virologically suppressed on stable ART, limiting suitable patients in clinical practice. There are also risks of resistance with the long acting regimen, particularly when starting and stopping treatment and in missing injections. For these reasons, patients must be carefully selected. The 2-monthly injections would remove the burden of daily oral treatment but would require more regular clinic visits for administration, which may have implications for patients and the service. If treatment is limited to 2-monthly dosing, there is reduced flexibility for patients and the service and this may

be less appropriate for some patients considered at higher risk of virologic failure. [1-3] Clinical experts consulted by SMC considered that cabotegravir in combination with rilpivirine is a therapeutic advancement due to its long-acting injectable formulation.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing cabotegravir in combination with rilpivirine prolonged-release injection and nine pooled daily oral antiretroviral therapies (ARTs) for the treatment of (HIV-1) infection in adults who are virologically suppressed and on a stable antiretroviral regimen, consistent with the clinical case. The included ARTs were the following single-tablet regimens: abacavir/dolutegravir/lamivudine (Triumeq®), bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya®), darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza®), emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey®), dolutegravir/lamivudine (Dovato®), dolutegravir/rilpivirine (Juluca®) and two multi-tablet regimens: emtricitabine/tenofovir alafenamide plus dolutegravir (Descovy® plus Tivicay®) and emtricitabine/tenofovir alafenamide plus raltegravir (Descovy® plus Isentress®). The analysis adopted a life-time horizon of 80 years.

The economic analysis incorporated a hybrid Markov model with a decision-tree to determine viral load (suppressed <50 copies/mL; unsuppressed ≥50 copies/mL), a Markov model with 5 health states based on CD4+ count, a transmission module and monthly cycles. Additionally, there was an all-absorbing death state in the model.

In the analysis, patients received oral cabotegravir together with oral rilpivirine in the first month, followed by two monthly initiation injections and injections every two months (Q2M) thereafter or daily oral ARTs until discontinuation due to virologic (failure switch) or non-virologic (stable switch) reasons at rates observed for cabotegravir plus rilpivirine in ATLAS-2M. Up to three subsequent lines of oral ARTs were modelled following first-line discontinuation.

Equivalence of clinical efficacy was assumed as a starting point for all treatments included in the economic analysis based on results from ATLAS-2M and an indirect treatment comparison of cabotegravir plus rilpivirine and oral ARTs. However, efficacy in the ARTs arm was later adjusted by 0.73 to account for perceived lower adherence rates associated with oral therapies in HIV. The adjustment factor was derived based on evidence from two published studies.[9, 10] Transition probabilities in the CD4+ count health states in the Markov model in first line were derived using data from ATLAS-2M in both arms, followed by transition probabilities from the published literature in subsequent treatment lines where “failure switch” patients were assigned a less favourable efficacy profile due to the potential for development of resistance.[11, 12] Additionally, discontinuation rates in subsequent lines were also obtained from the same sources and “failing switch” patients were assigned a substantially higher discontinuation rate in the first year. General population all-cause mortality was modelled and adjusted for treatment-specific mortality based on CD4+ count.

The model also included a transmissions module where virologically unsuppressed patients were assumed to be able to transmit the virus based on individual characteristics categorized in 5 populations. The population-specific characteristics were number of sexual partners, probability of condom use, condom effectiveness in the three populations who do not inject drugs. In the two populations who do inject drugs, monthly injection frequencies and probability of sharing needles was also included.

Health-state specific utility weights were obtained from the published literature.[13] The study used SF-6D data and included patient demographics, regimen attributes, disease status and AEs using a mixed effects maximum likelihood model. Additionally, an annual utility decrement was applied in the comparator arm based on findings from ATLAS and FLAIR studies of a statistically significant quality of life benefit for cabotegravir plus rilpivirine. No utility decrements associated with adverse events were included in the analysis as those were assumed to be already captured.

Aside from medicine acquisition costs, other costs included were those associated with administration and treatment of injection site reactions in the cabotegravir in combination with rilpivirine arm only, other AE treatment costs, HIV-specific costs (including opportunistic infection treatment costs), transmissions, costs of subsequent ARTs and end of life care costs.

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 simple discount was offered on the list price for cabotegravir plusrilpivirine. A PAS is also in place for the following oral ART therapies: abacavir/dolutegravir/lamivudine (Triumeq®), bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya®), dolutegravir/lamivudine (Dovato®),dolutegravir/rilpivirine (Juluca®) and dolutegravir (Tivicay®) .

The base case results are shown in Table 2, with key scenario analyses shown in Table 3. The results presented do not take account of the PAS for cabotegravir in combination with rilpivirine or any oral ARTs in the pooled comparator or subsequent treatments but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company, which used an estimate of the PAS price due to commercial confidentiality and competition law issues. As such, results are presented below using list prices for all medicines.

Table 2 Base case results (list price for all medicines)

Comparator	**ICER (£/QALY)**
Pooled oral ARTs	
cabotegravir plus rilpivirine	£21,396
ART: antiretroviral therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year	

The most substantial ICER increases from the presented scenarios in table 3 below were associated with assumptions around adherence rates impact on efficacy and treatment disutility in the oral ARTs arm.

Table 3: Selected scenario analyses (list price for all medicines)

	Scenario	Parameter variation	ICER (£/QALY)
0	Base case	-	£21,396
1	Adherence	Not modelled	£40,004
2	Comparator disutility	Half of base case estimate	£26,607
		Quarter of base case estimate	£23,719

ART: antiretroviral therapy; CAB: cabotegravir; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RPV: rilpivirine

The submitting company also presented a cost-minimisation analysis upon request, with comparisons against both a pooled comparator (weighted by market share data from NHS England) and individual oral ARTs. SMC is unable to publish these results at PAS or list price due to the company's requirement for commercial confidentiality.

Key limitations with the analysis include:

- Application of an adjustment factor to efficacy in the comparator arm to account for lower adherence rates associated with daily oral therapies is potentially inappropriate and the associated quality of life gain for cabotegravir in combination with rilpivirine is uncertain. Clinical experts consulted by SMC noted that the low adherence rate assumed in the model (74.4%) is not relevant to the Scottish population where patients are treated and monitored in specialist care. Additionally, the experts noted that small differences in adherence would not necessarily have a negative impact on efficacy. Indeed, statistics reported by Waverly care indicate that Scotland met the UK-wide 90-90-90 target (90%-diagnosed, of which 90% on treatment of which 90% with viral suppression) in 2019.[14] It was reported that 91% were diagnosed, 98% of them accessed treatment and 94% of them had undetectable viral load in Scotland. These goals were set in 2015 and the referenced study in the company submission where the adherence rates were obtained from was published in 2011 which indicates it is potentially an outdated source. Additionally, the considered patient population in this submission needs to be virologically suppressed and with no history of resistance to be eligible for cabotegravir in combination with rilpivirine which indicates that these patients may not have issues with adherence. The adjustment of efficacy in the oral ARTs arm also leads to a small survival gain in the cabotegravir arm which is uncertain given no indication of any survival benefit in the trial data (due to short follow-up period) and considered potentially inappropriate by some of the clinical experts consulted by SMC. Not modelling adherence reduces the incremental benefit substantially and increases the ICER (table 3, scenario 1).
- There are uncertainties with the modelled additional benefit associated with the treatment with cabotegravir plus rilpivirine. The utility values were based on SF-6D, which is an acceptable measure but may result in different utility estimates to the more commonly used EQ-5D. Trial data at 24 weeks showed a small but statistically significant improvement in

patients' quality of life which has been applied annually in the model as a treatment disutility in the comparator arm. Although it is expected that the substantially less frequent administration of HIV medicine which cabotegravir plus rilpivirine offer may have a positive impact on quality of life for patients, it is unclear if the benefit has been incorporated into the model correctly. Varying this model parameter leads to an increase in the ICER (table 3, scenario 2).

- There is a potential issue with the costs of administration in the cabotegravir arm included in the analysis. The cost was based on 15 minutes of nurse time and is most likely an underestimation given that clinic appointments are also associated with overhead costs. Additionally, some clinical experts consulted by SMC indicated that there might be additional resource implications associated with more frequent clinic visits for patients treated with cabotegravir plus rilpivirine.
- There are issues with the treatment costs included in the economic analysis. The cost of the comparator should preferably be estimated as a weighted average using relevant market share data rather than a simple average due to various PAS discounts associated with a number of oral ARTs. However, the company advised that such data are not available for Scotland. Therefore, given the current evidence of similar clinical efficacy, issues with costs and relevance of various ARTs as comparators, and the uncertain modelled quality of life incremental benefit, the NDC considered cost-minimization analyses of cabotegravir plus rilpivirine against most available oral ARTs individually as most appropriate economic analyses for decision-making.

Despite these limitations, the economic case was considered demonstrated.

Summary of patient and carer involvement

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

- We received patient group submissions from HIV Scotland, the National AIDS Trust (NAT) and Waverley Care. All three organisations are registered charities.
- HIV Scotland has received 35.5% pharmaceutical company funding in the past two years, including from the submitting company. NAT has received 15% pharmaceutical company funding in the past two years, including from the submitting company. Waverley Care has received 0.5% pharmaceutical company funding in the past two years, including from the submitting company.
- While advances in treatment have transformed HIV into a manageable, long-term condition, many people continue to face poor health and wellbeing linked to their diagnosis. Stigma and discrimination remain widespread, which not only has a damaging impact on the health and wellbeing of people living with HIV, but also undermines efforts to reduce transmission. The burden of treatment can have the greatest impact on people's daily lives.

- Pill-based regimens can be difficult to follow for a variety of reasons, including difficulty related to privacy and confidentiality. Adherence to treatment is vital to ensure the health and wellbeing of the person living with HIV, and to prevent transmission of the virus.
- Cabotegravir would give people living with HIV a greater choice in their treatment options. As a two monthly injection it could help remove the fear of hiding pill-based treatments and give greater freedom from rigorous treatment plans, helping them adhere to treatment. It would also be helpful for those with swallowing difficulties or a high pill burden. In addition, it could help those who are homeless or with no fixed address access treatment. Family members, carers and intimate partners of people living with HIV could also be positively affected by this treatment. Some concerns were raised regarding increasing the number of clinic visits required, and how this would impact on personal and professional commitments.

Additional information: guidelines and protocols

The British HIV association (BHIVA) published in 2015 'BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015' and there was an interim update published in 2016.[8] These predate the availability of cabotegravir and are currently being reviewed. For patients starting HIV treatment, these guidelines recommend a preferred backbone of tenofovir-DF/emtricitabine or tenofovir-AF/emtricitabine plus a third agent from ritonavir-boosted protease inhibitor, NNRTI or INI. There are recommendations on switching individual medicines to manage toxicity, improve adherence, manage potential drug interactions, or for individual preference or cost reasons. However there is currently no guidance on switching from a regimen of three medicines to two medicines or from orally to parenterally.

Additional information: comparators

Oral antitretroviral therapy, including single tablet combination products.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
cabotegravir	**cabotegravir 600mg by intramuscular injection every 2 months**	**10,905 in year 1** **10,066 in subsequent years**
(given with rilpivirine)	**rilpivirine 900mg by intramuscular injection every 2 months**	**2,884**

Costs from company submission. Costs in year 1 include the oral lead-in required when starting therapy. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 719 patients eligible for treatment with cabotegravir prolonged suspension in year 1 and 791 patients in year 5.

SMC is unable to publish the uptake rate or 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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

References

1. ViiV Healthcare. Cabotegravir prolonged release suspension for injection (Vocabria). Summary of Product Characteristics. European Medicines Agency. www.ema.europa.eu last accessed [01.07.21].

2. Janssen-Cilag International. Rilpivirine prolonged release suspension for injection (Rekambys). Summary of Product Characteristics. European Medicines Agency. www.ema.europa.eu. last accessed [27.07.21].

3. European Medicines Agency (EMA): European Public Assessment Report (EPAR). Cabotegravir (Vocabria®). 15/10/2020, EMEA/H/C/004976/0000 available at: http://www.ema.europe.eu/ [15 October 2020].

4. Orkin C, Arasteh K, Gorgolas Hernandez-Mora M, Pokrovsky V, Overton ET, Girard PM*, et al.* Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. New England Journal of Medicine. 2020;382(12):1124-35.

5. Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masia M*, et al.* Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. New England Journal of Medicine. 2020;382(12):1112-23.

6. Overton ET, Richmond G, Rizzardini G, Jaeger H, Orrell C, Nagimova F*, et al.* Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. The Lancet. 2020;396(10267):1994-2005.

7. Rizzardini G, Overton ET, Orkin C, Swindells S, Arasteh K, Gorgolas Hernandez-Mora M*, et al.* Long-Acting Injectable Cabotegravir + Rilpivirine for HIV Maintenance Therapy: Week 48 Pooled Analysis of Phase 3 ATLAS and FLAIR Trials. Journal of acquired immune deficiency syndromes (1999). 2020;85(4):498-506.

8. British HIV Association (BHIVA). BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). 2016 Aug 2016 [cited; Available from: https://www.bhiva.org/file/RVYKzFwyxpgiI/treatment-guidelines-2016-interim-update.pdf.

9. Cooper V, Moyle GJ, Fisher M, et al. Beliefs about antiretroviral therapy, treatment adherence and quality of life in a 48-week randomised study of continuation of zidovudine/lamivudine or switch to tenofovir DF/emtricitabine, each with efavirenz. AIDS Care. 2011;23(6):705-13.

10. GlaxoSmithKline/ViiV Healthcare. Cost-Effectiveness Model for Dolutegravir (ARAMIS-DTG) in Treatment-Experienced HIV Patients Report Version 3.0. 2013.

11. Kanters S, Socias ME, Paton NI, et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. The Lancet HIV. 2017;4(10):e433-e41.

12. Baril J-G, Angel JB, Gill MJ, et al. Dual Therapy Treatment Strategies for the Management of Patients Infected with HIV: A Systematic Review of Current Evidence in ARV-Naive or ARV-Experienced, Virologically Suppressed Patients. PLoS One. 2016;11(2):e0148231-e.

13. Kauf TL, Roskell N, Shearer A, et al. A predictive model of health state utilities for HIV patients in the modern era of highly active antiretroviral therapy. Value Health. 2008;11(7):1144-53.

14. https://www.waverleycare.org/news/update-hiv-scotland#:~:text=Scotland%20met%20the%2090%2D90,with%20an%20undetectable%20viral%20load.

This assessment is based on data submitted by the applicant company up to and including 12 August 2021.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.