SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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# dolutegravir 50mg / rilpivirine 25mg film-coated tablets (Juluca®) SMC2091

## ViiV Healthcare Ltd.

10 August 2018

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 NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**dolutegravir / rilpivirine film-coated tablet (Juluca®)** is accepted for use within NHSScotland.

**Indication under review:** 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 for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor.

Dolutegravir plus rilpivirine was shown to be non-inferior to antiretroviral regimens containing a dual nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone plus a third agent (integrase inhibitor, protease inhibitor or NNRTI) in maintaining plasma HIV-1 RNA <50 copies/mL in two phase III randomised studies in virologically-suppressed adults.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of dolutegravir / rilpivirine. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

**Chairman**
**Scottish Medicines Consortium**

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## Indication

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 for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INSTI).[1]

## Dosing Information

One tablet once daily with a meal. It is recommended that the film-coated tablet be swallowed whole with water and not be chewed or crushed.[1]

Dolutegravir / rilpivirine should be prescribed by physicians experienced in the management of HIV infection.[1]

## Product availability date

04 June 2018

## Summary of evidence on comparative efficacy

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle.[1] Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 and its activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase.[1] Dolutegravir / rilpivirine is a fixed dose combination tablet and is the first two-medicine complete regimen for HIV-1 to be licensed and is indicated as maintenance therapy in virologically suppressed adults who are currently stabilised on antiretroviral therapy (ART).

The evidence supporting the licensing of dolutegravir / rilpivirine is from two identically designed, ongoing, phase III, open-label, randomised, non-inferiority studies, SWORD-1 and SWORD-2. The studies recruited patients ≥18 years old, who were on their first or second ART regimen, with stable viral suppression (viral load <50 copies/mL) for ≥6 months at screening. They were required to have no observed instance of viral load >50 copies/mL in the 6-month period before screening and no more than one instance of viral load >50 copies/mL but <200 copies/mL in the previous period of 6 to 12 months before screening. Prior ART regimens consisting of two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus a third medicine (NNRTI, integrase inhibitor [INSTI] or protease inhibitor [PI]) were allowed, including pharmacokinetically boosted PIs or unboosted atazanavir. Enrolment of patients with current or previous exposure to dolutegravir or rilpivirine was limited to about 10%.[2]

Pooled analysis was pre-defined. Across both studies, patients were screened and randomised in a 1:1 ratio to switch from their current antiretroviral regimen (CAR) to dolutegravir 50mg plus rilpivirine 25mg once daily with a meal; or to remain on their CAR for 52 weeks. At week 48, patients who were assigned to continue their CAR were assessed and those who remained virologically suppressed switched to dolutegravir plus rilpivirine at week 52 and were to be followed to week 148. Randomisation was stratified by third-agent class (INSTI or NNRTI or PI), age (<50 years or ≥50 years), and planned participation in a bone mineral density sub-study.[2]

The primary outcome was the proportion of patients with HIV plasma viral load <50 copies/mL at week 48 using the US Food and Drug Administration (FDA) snapshot algorithm. The primary analysis

population was the intention to treat exposed (ITT-E) population (all randomised patients who received at least one dose of study treatment; n=1,024). Non-inferiority of dolutegravir plus rilpivirine in maintaining plasma HIV-1 RNA <50 copies/mL was demonstrated in the ITT-E population of both SWORD studies separately (non-inferiority margin -10%) and in the pre-defined pooled analysis (non-inferiority margin -8%).[2, 3] A sensitivity analysis was conducted in the per protocol population (ITT-E population excluding patients with protocol violations that could affect the assessment of antiviral activity or patients who received the correct study medication for <90% of total time on treatment; n=910).[2] See Table 1 for results of the primary outcome.

**Table 1: Proportion of patients with HIV plasma viral load <50 copies/mL at week 48[3]**

| | Dolutegravir and Rilpivirine | Current antiretroviral regimen | Adjusted treatment difference (95% CI) |
|---|---|---|---|
| **SWORD-1 (ITT-E)** | 95% (240/252) | 96% (245/256) | -0.6% (-4.3% to 3.0%) |
| **SWORD-2 (ITT-E)** | 94% (246/261) | 94% (240/255) | 0.2% (-3.9% to 4.2%) |
| **Pooled analysis (ITT-E)** | 95% (486/513) | 95% (485/511) | -0.2% (-3.0 to 2.5) |
| **Pooled analysis (PP)** | 96% (437/457) | 96% (435/453) | -0.7% (-3.3 to 1.8) |

ITT-E=intention to treat exposed; PP=per protocol; CI=confidence interval

Secondary outcomes included snapshot virological failure rates in the dolutegravir plus rilpivirine and CAR groups, which demonstrated a treatment difference of -0.5% (95% CI: -1.4 to 0.5); therefore non-inferiority of this outcome was demonstrated based on a pre-defined margin of 4%. Median CD4 cell counts increased from baseline to week 48, by 28 cells/microlitre, (interquartile range [IQR] -55.0 to 112.5) in the dolutegravir plus rilpivirine group versus 22 cells/microlitre, (IQR -46 to 108) in the CAR group.[2]

Patient reported outcomes included the HIV Treatment Satisfaction Questionnaire, status version (HIVTSQs) and the Symptom Distress Module.[2] The HIVTSQ is a 10-item self-reported scale that measures overall satisfaction with treatment and by specific domains eg convenience and flexibility. Each item is scored 0 to 6 where a higher score indicates greater improvement in the past few weeks. These items are summed to produce a treatment satisfaction total score (0 to 60) and two subscales: general satisfaction / clinical subscore and lifestyle / ease subscore (0 to 30).[4] Mean HIVTSQs total scores increased (improved) by 1.5 points from a baseline of 54.4 (standard deviation [SD] ±6.4) in the dolutegravir plus rilpivirine group and by 0.4 points from a baseline of 53.9 (SD ±6.6) in the CAR group, (statistical significance not reported). Compared with CAR, there was a small significant improvement in change from baseline to week 48 in the dolutegravir plus rilpivirine group for the lifestyle / ease subscore.[2] The Symptom Distress Module is a 20-item self-reported measure that evaluates the presence and perceived distress linked to symptoms commonly associated with HIV or its treatment. The symptom bother score (range 0 to 80) includes a score for each symptom present ranging from 1 (it doesn't bother me) to 4 (it bothers me a lot).[4] There was a significant improvement in the reduction in mean symptom bother score in the dolutegravir plus rilpivirine group compared with the CAR group.[2] It is not clear if these improvements in quality of life were clinically significant. Patient reported adherence was assessed using a visual analogue scale and was high, with no difference between the dolutegravir plus rilpivirine group (97.8%) and the CAR group (98.3%).[2]

A sub-study (DEXA) of the SWORD 1 and 2 studies evaluated change from baseline in bone mineral density following the switch from a triple antiretroviral regimen containing tenofovir disoproxil fumarate to dolutegravir plus rilpivirine.[3] Mean bone mineral density increased from baseline to week 48 in

patients who switched to dolutegravir plus rilpivirine (1.34% total hip and 1.46% lumbar spine) compared with those who continued on treatment with a tenofovir disoproxil fumarate-containing antiretroviral regimen (0.05% total hip and 0.15% lumbar spine). Any beneficial effect on fracture rate was not studied.[1]

A randomised, open-label, two-period, single dose, crossover study (201676) in 118 healthy adults concluded that dolutegravir 50mg / rilpivirine 25mg fixed dose combination tablet is bioequivalent to the single components administered separately.[3]

## Summary of evidence on comparative safety

In the pooled analysis of SWORD 1 and SWORD 2, at 48 weeks, adverse events were reported in 77% (395/513) of patients receiving dolutegravir plus rilpivirine compared with 71% (364/511) receiving CAR.[2] The most commonly reported adverse events were nasopharyngitis, headache, upper respiratory tract infection, diarrhoea, back pain, bronchitis, influenza, and arthralgia. Most of these were of grade 1 severity with very few grade 2 or worse events in these categories.[2]

Treatment-related adverse events reported in ≥2% of patients in either group occurred in 19% (97/513) of patients receiving dolutegravir plus rilpivirine versus 1.8% (9/511) of patients receiving CAR and these were categorised as serious events in 0.8% (4/513) versus 0.2% (1/511) of patients in the respective groups. Adverse events that lead to withdrawal by 48 weeks occurred in 3.3% (17/513) of patients receiving dolutegravir plus rilpivirine versus 0.6% (3/511) of patients receiving CAR.[2]

Neuropsychiatric adverse events were reported more frequently in the dolutegravir plus rilpivirine group than in the CAR group; 12% (61/513) versus 6.3% (32/511), respectively. The most frequent of these were insomnia, depression, anxiety and abnormal dreams; and there were steady incremental increases in these events at weeks 4, 12 and 24. Treatment-related neuropsychiatric adverse events were reported in 5.0% (26/513) of patients in the dolutegravir plus rilpivirine group versus 0.4% (2/511) of patients in the CAR group.[2]

The European Medicines Agency (EMA) is evaluating preliminary results from an observational study that revealed an increased risk of neural tube defects in infants born to women who took dolutegravir at the time of conception.[5]

## Summary of clinical effectiveness issues

HIV-1 infection causes the immune system to be chronically activated and CD4+ T cells gradually decrease in number resulting in acquired immunodeficiency syndrome (AIDS). Viral load (concentration of HIV-1 RNA in the blood) is a predictor of disease progression. Treatment aims to suppress, and subsequently maintain, the HIV-1 viral load below 50 copies/mL (limit of detection of most commonly used assays).[3] Current standard therapy usually includes two NRTIs plus a third agent (PI, NNRTI, or INSTI). Preferred NRTIs are tenofovir disoproxil / emtricitabine or tenofovir alafenamide / emtricitabine. Preferred third agents are ritonavir boosted atazanavir; ritonavir boosted darunavir; dolutegravir; cobicistat boosted elvitegravir; raltegravir or rilpivirine.[6] Dolutegravir / rilpivirine is licensed as a two-medicine complete regimen. Both component medicines are currently licensed, and accepted by SMC, for use in combination with other antiretroviral drugs for the treatment of HIV-1.[7-11] Dolutegravir / rilpivirine avoids the need for a traditional two NRTI backbone regimen with associated toxicities.

The pivotal studies used single entity dosage forms of dolutegravir and rilpivirine, however a pharmacokinetic study demonstrated the bioequivalence of dolutegravir / rilpivirine fixed dose

combination tablet (Juluca®).[3] Dolutegravir plus rilpivirine was shown to be non-inferior to CAR in maintaining plasma HIV-1 RNA <50 copies/mL at week 48 in both SWORD studies.[3] Long-term data on this dual therapy regimen are awaited for this life-long condition.

The submitting company has proposed that dolutegravir / rilpivirine represents a potential advantage in reducing short and long-term toxicity compared with standard regimens that contain three or four medicines, especially as the HIV population is ageing and there is concern about co-morbidities and polypharmacy. However, in the SWORD studies dolutegravir / rilpivirine had a worse safety profile than the CAR regimens.[2] Whilst it is acknowledged that patients who start a new treatment may be expected to experience more initial adverse events than those who continued on their stable CAR, an improved safety profile versus CAR has not been demonstrated. Another potential concern is that a safety alert was issued by the EMA on 18 May 2018 concerning reports of birth defects in babies born to women who became pregnant while taking dolutegravir.[5]

Over three quarters of the study patients were in Center for Disease Control and Prevention (CDC) category A (asymptomatic, lymphadenopathy or acute HIV). It is not known if the same results would be seen in patients with more advanced disease; (category B = symptomatic, not AIDS; category C = AIDS).[2]

The DEXA sub-study found a significant increase in mean bone mineral density from baseline to week 48 in patients who switched from a triple antiretroviral regimen containing tenofovir disoproxil fumarate to dolutegravir plus rilpivirine compared with those who continued on treatment with tenofovir disoproxil fumarate-containing ART. However there is, at present insufficient evidence to claim any beneficial effect on bone metabolism, bone stability and fracture rate and the long-term clinical effects of these changes are therefore unknown.[3]

The submitting company has proposed that the primary comparators of dolutegravir / rilpivirine are the following branded regimens:

- Emtricitabine / tenofovir alafenamide (Descovy®) in combination with either an INSTI (dolutegravir or raltegravir) or a boosted PI (darunavir / ritonavir or darunavir / cobicistat).
- Evitegravir / cobicistat / emtricitabine / tenofovir alafenamide (Genvoya®)
- Rilpivirine / emtricitabine / tenofovir alafenamide (Odefsey®)

The comparator arms of the SWORD 1 and 2 studies comprised a variety of different antiretroviral regimens. At screening, 72% of all study patients were receiving tenofovir disoproxil fumarate and 68% were receiving emtricitabine as backbone treatment. The most common third agent class was NNRTI (54%); then PI (26%) and then INSTI (20%).[2] All of these proposed primary comparator regimens include tenofovir alafenamide, but no patients received this medicine in the SWORD 1 and 2 studies as the studies pre-dated its availability.[3]

Clinical experts consulted by SMC highlighted that dolutegravir / rilpivirine offers the option of a NRTI sparing regimen within a single tablet which would be of benefit in patients with resistance to NRTIs or where the NRTI class is not advisable e.g. due to advanced kidney failure or drug interactions.

## Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis which compared dolutegravir / rilpivirine against a range of comparators in the licenced indication. Comparators were divided into primary and secondary comparators with primary comparators considered by the company to be medicines dolutegravir / rilpivirine would most likely offer an alternative to in clinical practice. Secondary comparators were noted

as less likely to be displaced by dolutegravir / rilpivirine but remained clinically relevant according to clinical experts consulted by the submitting company.

Primary comparators included branded regimens containing tenofovir alafenamide:

- emtricitabine / tenofovir alafenamide (Descovy®) in combination with either dolutegravir or raltegravir
- emtricitabine / tenofovir alafenamide (Descovy®) in combination with darunavir + ritonavir
- elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide (Genvoya®)
- rilpivirine / emtricitabine / tenofovir alafenamide (Odefsey®)

Secondary comparators included:

- emtricitabine / tenofovir disoproxil fumarate (Truvada®) in combination with either dolutegravir or raltegravir
- emtricitabine / tenofovir disoproxil fumarate (Truvada®) in combination with rilpivirine or as a single tablet regimen of emtricitabine / tenofovir disoproxil fumarate / rilpivirine (Eviplera®)
- abacavir / lamivudine (Kivexa®) in combination with raltegravir
- dolutegravir / abacavir / lamivudine (Triumeq®)
- elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide (Genvoya®)

The clinical data used to support comparable efficacy of dolutegravir / rilpivirine versus the comparators included the SWORD-1 and SWORD-2 studies. The company stated that the non-inferiority of dolutegravir / rilpivirine versus current antiretroviral therapy (CAR) (inclusive of the comparators captured in the economic evaluation) was demonstrated in the SWORD -1 and 2 studies and dolutegravir / rilpivirine demonstrated durable efficacy with continued virological suppression through to 100 weeks.

Medicines costs only were included in the analysis. The company assumed the decision to initiate treatment with dolutegravir / rilpivirine would be made as part of a routine follow-up appointment in secondary care, and subsequent appointments would be similar to the other comparators. Therefore no impact on resource use was assumed and the only costs included in the analysis were medicine costs.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. PAS discounts are in place for dolutegravir, dolutegravir / abacavir / lamivudine (Triumeq®) and elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide (Genvoya®) and these were included in the results used for decision-making by the SMC by using estimates of the comparator PAS prices.

The base case results for dolutegravir/ rilpivirine against the primary comparators are listed below in Table 2. Please note that the results in Table 2 use list prices for all medicines.

**Table 2: Base case results (list prices)**

| Medicine | Total Cost (£) | Incremental cost/saving (£) |
|---|---|---|
| dolutegravir/ rilpivirine | £8,504.74 | |
| emtricitabine / tenofovir alafenamide (Descovy®) + dolutegravir | 10,396.17 | -1,891.43 |
| emtricitabine / tenofovir alafenamide (Descovy®) + raltegravir | 10,063.54 | -£1,558.79 |
| emtricitabine / tenofovir alafenamide (Descovy®) + darunavir +ritonavir | 8,187.80 | £316.94 |
| elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide (Genvoya®) | 10,700.71 | -2,195.96 |
| rilpivirine / emtricitabine / tenofovir alafenamide (Odefsey®) | 6,399.06 | £2,105.69 |

The company provided sensitivity analysis which explored the impact of additional follow-up appointments on the results (including a threshold analysis). In addition, the company presented sensitivity analyses upon request which included adverse event costs in the economic model, and a separate analysis which included treatment discontinuation as well as subsequent therapy in the analysis. When using list prices for dolutegravir / rilpivirine and comparator medicines, the conclusions were relatively similar to the base case.

Results comparing dolutegravir / rilpivirine against the secondary comparators are listed below in Table 3. Please note that the results in Table 3 use list prices for all medicines.

**Table 3. Secondary comparators (list prices)**

| Medicine | Total Cost (£) | Incremental cost/saving (£) |
|---|---|---|
| dolutegravir / rilpivirine | 8,507.74 | |
| emtricitabine /tenofovir disoproxil fumarate (Truvada®) + dolutegravir | 10,396.17 | -1,891.43 |
| emtricitabine / tenofovir disoproxil fumarate (Truvada®) + raltegravir | 10,063.54 | -1,558.79 |
| abacavir / lamivudine (Kivexa®) + raltegravir | 9,378.31 | -873.57 |
| dolutegravir/ abacavir / lamivudine (Triumeq®) | 9,710.95 | -1,206.20 |
| elvitegravir /cobicistat / emtricitabine / tenofovir alafenamide (Genvoya®) | 10,700.71 | -2,195.96 |
| emtricitabine /tenofovir disoproxil fumarate (Truvada®) + rilpivirine | 6,764.67 | 1,740.08 |
| emtricitabine /tenofovir disoproxil fumarate/rilpivirine (Eviplera®) | 6,399.06 | 2,105.69 |

Upon request the company provided sensitivity analysis which used published generic prices for emtricitabine / tenofovir disoproxil fumarate (Truvada®) and abacavir / lamivudine (Kivexa®). Using list prices for dolutegravir / rilpvirine and comparator medicines, dolutegravir / rilpvirine was more costly than most secondary comparators when applying generic prices in the economic model.

The results presented above do not take account of the PAS for dolutegravir, dolutegravir / abacavir / lamivudine (Triumeq®) and elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide (Genvoya®) and when an estimate of the PAS was included, dolutegravir / rilpivirine became less cost-effective.

SMC is unable to present the results provided by the company which used an estimate of the PAS price for dolutegravir, dolutegravir / abacavir / lamivudine (Triumeq®) and elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide (Genvoya®) due to commercial confidentiality and competition law issues.

The main weaknesses were

- The analysis presented is a simple cost-minimisation analysis which focused on medicine costs only. Adverse events or discontinuation/subsequent treatments were not included in the base case analyses which is an appropriate assumption in relation to the chosen format of the analysis, i.e. a simple cost-minimisation. However, not including differences in adverse events and discontinuation may not be appropriate if dolutegravir / rilpivirine has a worse safety profile and higher discontinuation rate than the CAR regimens. The company subsequently provided sensitivity analyses which included adverse event costs and treatment discontinuation/subsequent therapy in the economic model and these analyses did not affect the overall conclusion.
- There may be some concerns related to the assumption of non-inferiority between dolutegravir / rilpivirine and the primary (or even secondary) comparators. This is because the comparators in the economics were not always reflective of the medicines received in the CAR arm of the SWORD studies. However, following consideration of SMC expert responses, the SWORD studies were considered appropriate to support a cost-minimisation analysis.
- In relation to the secondary comparators, some medicines are available as generic medicines and the company did not include the generic costs in the base case results. However, as described above the company provided additional analyses which used published generic prices for emtricitabine / tenofovir disoproxil fumarate (Truvada®) and abacavir / lamivudine (Kivexa®) in the economic model. The results from these analyses support use of dolutegravir / rilpivirine as an option in patients unsuitable for generic regimens.

Despite the above uncertainties the economic case has been demonstrated.

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

## Summary of patient and carer involvement

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

- We received a patient group submission from Waverley Care and HIV Scotland, both are registered charities.
- In the last two years, Waverley Care has received 2% of its funding, and HIV Scotland 3.5% of its funding from the pharmaceutical industry. However, neither have received funding from the submitting company.
- A diagnosis of HIV is associated with high levels of stigma, discrimination and shame, which can destroy relationships and weaken peoples resolve to start and stay on treatment. Many older patients are also faced with age-related co-morbidities and managing these in addition to keeping their HIV under control can be challenging and can involve a large number of different medications.
- Although there are currently effective and well tolerated treatments available in Scotland, patients have raised concerns that the long-term use of these medications could result in adverse effects, such as loss of bone density. In addition, medication regimes that involve large numbers of; large, hard to swallow, tablets can be a real struggle for some patients.
- There is a need for ongoing simplification of medications, as the easier a medication is to take, the more likely people will be to adhere to treatment. Dolutegravir / rilpivirine broadens the treatment options available to patients and offers a simplified and effective regime, which could

reduce pill burden and potentially reduce the adverse effects on bone density. The combination of which, could promote adherence to treatment and help patients maintain full viral suppression in the long term.

## Additional information: guidelines and protocols

Both guidelines cited below predate the availability of the medicine under review which is the first licensed two-drug regimen for HIV. The guidance on switching refers to individual medicines. There is no current guidance on switching from a regimen of three medicines to one of two medicines.

The British HIV Association (BHIVA) published guidance on the treatment of HIV-1 positive adults with ART in 2015 and the guidance was updated in 2016.[6] This guideline notes that, for people taking fully virally suppressive regimens, switching individual components of the ART combination regimen may be considered to manage toxicity, improve adherence, manage potential drug interactions, or for individual preference or cost reasons. Switching should not be at the cost of virological efficacy. Before switching, consideration should be given to differences in side-effect profile, drug interactions, drug-resistance patterns and effect of food. In individuals with previous NRTI resistance mutations, there is a recommendation against switching a ritonavir boosted PI to either an NNRTI or an INSTI as the third agent.[6]

The European Aids Clinical Society published Guidelines in October 2017.[12] These provide recommendations on switch strategies for virologically suppressed persons including the situation of ageing and / or co-morbidity with a possible negative impact of medicines in the current regimen, e.g. on the risk of cardiovascular disease or metabolic parameters. The guidelines note that clinicians should always review possible adverse events or tolerability issues with current antiretroviral regimens. The objectives of treatment modification should be to eliminate or improve adverse events, facilitate adequate treatment of co-morbid conditions, and improve quality of life. The primary concern when switching should be to sustain and not to jeopardise virological suppression. In persons without prior virological failures and no archived resistance, switching regimens entail a low risk of subsequent failure if clinicians select one of the recommended combinations for first-line therapy. The majority of clinical trials showing non-inferiority of the new regimen after the switch have actively excluded persons with prior virological failures. A complete anti-retroviral history with HIV virological load, tolerability issues and cumulative genotypic resistance history should be analysed prior to any drug switch.

Before switching, remaining treatment options in case of potential virological failure of the new regimen should be taken into consideration. If the switch implies discontinuing tenofovir disoproxil and not starting tenofovir alafenamide, clinicians should check for negative hepatitis B virus status. HIV-positive persons should be monitored soon (e.g. 4 weeks) after treatment switch to check for maintenance of suppression and possible toxicity of the new regimen.

The guidelines include dual therapy with dolutegravir / rilpivirine as a class-sparing strategy and note that, in clinical trials these strategies have not been associated with more virological rebounds than triple therapy. [12]

## Additional information: comparators

A number of comparator regimens are in use in clinical practice. These usually include two NRTIs plus a third agent (PI, NNRTI, or INSTI). Primary comparators include the following branded regimens:

- Emtricitabine / tenofovir alafenamide (Descovy®) in combination with either an INSTI (dolutegravir or raltegravir) or a boosted PI darunavir / ritonavir or darunavir / cobicistat.
- Evitegravir / cobicistat / emtricitabine / tenofovir alafenamide (Genvoya®)
- Rilpivirine / emtricitabine / tenofovir alafenamide (Odefsey®)

## Cost of relevant comparators

| Medicine | Dose Regimen | Cost per year (£) |
|---|---|---|
| **Dolutegravir 50mg / Rilpivirine 25mg (Juluca®)** | **One tablet orally once daily** | **8,481*** |
| Elvitagravir 150mg / Cobistat 150mg / Emtricitabine 200mg / Tenofovir alafenamide 10mg (Genvoya®) | One tablet orally once daily | 10,671 |
| Emtricitabine 200mg / Tenofovir alafenamide 25mg (Descovy®)<br>plus<br>Dolutegravir 50mg | One tablet orally once daily<br><br>plus<br>One tablet orally once daily | 10,368 |
| Emtricitabine 200mg / Tenofovir alafenamide 25mg (Descovy®)<br>plus<br>Raltegravir 400mg or 600mg | One tablet orally once daily<br><br>plus<br>400mg orally twice daily or 2x600mg orally once daily | 10,034 |
| Emtricitabine 200mg / Tenofovir alafenamide 25mg (Descovy®)<br>plus<br>Darunavir 800mg<br>plus<br>Ritonavir 100mg | One tablet orally once daily<br><br>plus<br>One tablet orally once daily<br>plus<br>One tablet orally once daily | 8,165 |
| Darunavir 800mg / Cobistat 150mg / Emtricitabine 200mg / Tenofovir alafenamide 10mg (Symtuza®) | One tablet orally once daily | 8,165 |
| Rilpivirine 25mg / Emtricitabine 200mg / Tenofovir alafenamide 25mg (Odefsey®) | One tablet orally once daily | 6,382 |

*Doses are for general comparison and do not imply therapeutic equivalence. Cost of Juluca® from company submission; costs of Genvoya® and Odefsey® from eVadis on 28 May 2018; costs of other medicines from MIMS online on 11 June 2018. Costs do not take any patient access schemes into consideration. * The annual cost of Juluca® is the same as the combined cost of the constituents, rilpivirine 25mg and dolutegravir 50mg, given as individual medicines (based on costs from eVadis May 2018).*

## Additional information: budget impact

The company estimated that 460 patients were assumed to be eligible in year 1 rising to 581 in year 5 to which confidential uptake rates were applied.

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 commercially confidential.**

References


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This assessment is based on data submitted by the applicant company up to and including 11 July 2018.

**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 NHS Scotland 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 NHS Scotland 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.*