All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

# Final Appraisal Report

# Raltegravir (Isentress®▼) in combination with other antiretrovirals for the treatment of HIV-1 infection in adults

# Advice No: 1110

## Recommendation of AWMSG

**Raltegravir (Isentress®▼) is recommended in combination with other anti-retroviral medicinal products as an option for restricted use within NHS Wales for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients in accordance with British HIV Association (BHIVA) guidance.**

**Raltegravir (Isentress®▼) should be restricted for use in patients who are resistant or intolerant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) or for whom these options are compromised due to drug-drug interactions.**

**Current AWMSG advice, No 1808, in relation to the use of raltegravir (Isentress®▼) in treatment-experienced adult patients with human immunodeficiency virus (HIV-1) infection remains unchanged.**

**AWMSG is of the opinion that raltegravir (Isentress®▼) is not suitable for shared care within NHS Wales.**



This report should be cited as:

## 1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 23rd June 2010

**The recommendation of AWMSG is:**

Raltegravir (Isentress®▼) is recommended in combination with other anti-retroviral medicinal products as an option for restricted use within NHS Wales for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients in accordance with British HIV Association (BHIVA) guidance.

Raltegravir (Isentress®▼) should be restricted for use in patients who are resistant or intolerant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) or for whom these options are compromised due to drug-drug interactions.

Current AWMSG advice, No 1808, in relation to the use of raltegravir (Isentress®▼) in treatment-experienced adult patients with human immunodeficiency virus (HIV-1) infection remains unchanged.

AWMSG is of the opinion that raltegravir (Isentress®▼) is not suitable for shared care within NHS Wales.

## 2.0 PRODUCT DETAILS

### 2.1 Licensed indication
Raltegravir (Isentress®▼) is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients[1].

### 2.2 Dosing
The recommended dosage is 400mg administered twice daily with or without food[1].

### 2.3 Market authorisation date
9th September 2009[2]

### 2.4 UK Launch date
September 2009[2]

## 3.0 DECISION CONTEXT

### 3.1 Background
The British HIV Association (BHIVA) guidelines currently recommend that treatment should be started in patients who have a CD4 count of ≤350 cells/microL or at higher counts where there is a higher risk of clinical events e.g. due to co-morbidities such as hepatitis B or established cardiovascular disease[3].

For those initiating antiretroviral therapy, the aim of treatment is to achieve a viral load of <50 copies/mL within four to six months of starting treatment. Emtricitabine and tenofovir disoproxil (Truvada®) or abacavir and lamivudine (Kivexa®) (with specific precautions) should be used first line with efavirenz (Sustiva®). Boosted protease inhibitors (PIs) are reserved for specific groups of patients such as those with primary nucleoside reverse transcriptase inhibitor (NRTI) and/or non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance[3].

A change of therapy should be considered for any patient who experiences a sustained rebound in viral load levels. The choice of treatment should be guided by current and previous resistance testing, treatment history, patient adherence, drug tolerance and drug-drug interactions[3]. However, due to a range of factors, including pre-existing or newly developed antiretroviral resistance, responses may fail over time and subsequent regimens may be progressively less likely to produce a durable virological response. Highly pre-treated patients may not achieve the goals of undetectable and durable HIV plasma viral load suppression and immunological improvement[3].

Raltegravir is the first drug of a new class of antiretroviral agents, called integrase strand transfer inhibitors, to be licensed. It inhibits the catalytic activity of integrase, an HIV-encoded enzyme that is required for viral replication, thus inhibiting integration of the HIV genome into the host cell genome and preventing propagation of the viral infection[1]. Raltegravir was originally licensed in treatment experienced adults and received a positive recommendation by AWMSG in October 2008[4]. The licence was extended in September 2009, to include treatment naïve adults, however this company submission considers that the greatest need for raltegravir is amongst patients who are resistant or intolerant to NNRTIs or PIs or for whom these options are compromised due to drug-drug interactions[2]. The company estimate that there will be around 20 patients eligible for treatment in Wales in 2010[2]; this is in addition to the previous estimate for use in treatment-experienced adults alone[4].

### 3.2 Comparators

No other integrase inhibitors are currently licensed in the UK. Raltegravir is licensed for use in combination with other antiretrovirals[1] and therefore would be added to background therapy or in some situations would be used in addition to, rather than replacement of other antiretrovirals. For treatment-naïve patients, WMP-sought expert opinion indicated that efavirenz would be the most appropriate comparator [5]; however the company have focused this submission for use in those patients who are resistant, intolerant or have compromised treatment options due to drug-drug interactions[2]. The company suggest that enfuvirtide is therefore the most appropriate comparator[2]. It should be noted that the licence for enfuvirtide includes patients who have received treatment with and failed on regimens containing at least one medicinal product from each of the main antiretroviral classes (PI, NNRTI and NRTI), or who have intolerance to previous antiretroviral regimens[6] and therefore may not be fully comparative to raltegravir.

### 3.3 Guidance and related advice

- In 2008 the British HIV Association produced guidelines for the treatment of HIV-1 infected adults with antiretroviral therapy[3]. A consultation draft addendum to these guidelines was released in 2009[7].
- The London New Drugs Group, on behalf of the HIV Drug and Treatment sub group of the London HIV Consortium issued a review of raltegravir in October 2009[8].

## 4.0 EXECUTIVE SUMMARY

### 4.1 Review of the evidence on clinical effectiveness

The available evidence indicates that raltegravir is comparable in efficacy and safety to efavirenz when used in treatment-naïve patients (STARTMRK). Although changes in triglycerides, total, high density lipoprotein (HDL) and low density lipoprotein (LDL)-cholesterol were significantly smaller in the raltegravir group compared to the efavirenz group, the difference in total cholesterol/HDL cholesterol ratio was not significant. Raltegravir has also demonstrated superior efficacy and safety compared with placebo in highly treatment resistant HIV-1 infected patients (BENCHMRK). Non-inferiority was met in two short-term studies that switched virologically stable patients with multidrug resistant HIV-1 from enfuvirtide to raltegravir (CHEER and EASIER); safety was generally comparable for both treatments, although raltegravir was associated with higher incidences of abnormalities in lipid concentrations and liver function tests.

Concern has been raised regarding the development of resistance to integrase inhibitors when raltegravir is used with no fully active drugs in the optimised background regimen (OBR). This has been further highlighted with the results of the SWITCHMRK studies which were stopped early when the non-inferiority margin was not met following a switch from a boosted PI combination (lopinavir/ritonavir) to raltegravir. The licence recommends that where possible raltegravir should be administered with two other active antiretroviral drugs.

### 4.2 Review of the evidence on cost-effectiveness

A simple cost minimisation analysis (CMA) has been conducted to compare raltegravir against enfuvirtide in a select group of patients described by the company as those who are intolerant or resistant to NNRTIs or PIs or for whom these options are compromised due to drug-drug interactions. No evidence on the cost effectiveness of raltegravir in treatment-naïve patients is provided, nor in treatment-experienced patients who are candidates for other agents.

The analysis considers only annual drug acquisition costs, which are lower for raltegravir compared with enfuvirtide (£7,500 versus £13,400). It is implicitly assumed that raltegravir and enfuvirtide are equivalent in all dimensions of health outcome over a patient's lifetime, including effectiveness (e.g. survival), safety, tolerability, health-related quality of life and patient preferences. Only short term data are available to lend support to the non-inferiority of raltegravir compared with enfuvirtide in terms of virological and immunological response, and suggest differences in lipid profile in favour of enfuvirtide. The CMA approach precludes consideration of long-term costs or of potential differences in patient preferences related to routes of administration of raltegravir (twice daily oral administration) and enfuvirtide (twice daily subcutaneous injection).

### 4.3 Limitations of the evidence

- In treatment-naïve patients data is not available on the use of raltegravir in combination with PIs.
- No data has been presented on the use of raltegravir in patients unable to receive alternative antiretrovirals due to drug-drug interactions or significant co-morbidities.
- Comparative data between raltegravir and enfuvirtide are short term (24 week data) and in a limited number of patients.

## 5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

### 5.1 Clinical evidence

The company submission is based on clinical trial data from two treatment-naïve studies[9-11]; pooled data from two treatment-experienced studies[12-14] and four studies in subjects who were switched when virologically stable to raltegravir (efavirenz[15,16] and lopinavir/ritonavir[17]). Further results are available in tables 1A-C in appendix 1.

#### 5.1.1 Treatment naïve

PN004 was a phase II randomised, controlled trial comparing raltegravir in doses ranging from 100 to 600mg twice daily versus efavirenz 600mg once daily; all patients received a background of tenofovir 300mg once daily and lamivudine 300mg once daily. One hundred and ninety eight treatment-naïve patients were included in the analyses. The primary endpoint of the proportion of patients achieving plasma HIV-1 RNA level <400 copies/mL was measured at week 24. Plasma HIV-1 RNA levels were reduced to <400 copies/mL in 85% to 98% of patients receiving raltegravir (all doses) and efavirenz. Compared with efavirenz, raltegravir was associated with a more rapid decline in HIV-1 RNA levels, although results were comparable for both products at week 24. These results were maintained at week 48. From week 48 all patients receiving raltegravir were switched to 400mg twice daily (licensed dose), at week 96, 84% of patients in both groups had a HIV-1 RNA <400 copies/mL. Results were comparable for <50 copies/mL[9,10]. This study was not powered for formal efficacy comparisons between raltegravir and efavirenz.

STARTMRK was a double-blind, randomised, non-inferiority study in HIV treatment-naïve patients. Two hundred and eighty one patients received raltegravir 400mg twice daily and 282 received efavirenz 600mg once daily added to a background of tenofovir 300mg and emtricitabine 200mg once daily. Using a modified intention-to-treat (mITT) (non-completer = failure), the primary endpoint of HIV-1 RNA <50 copies/mL at week 48 was reached by 86.1% (n=241) in the raltegravir group compared with 81.9% (n=230) in the efavirenz group (difference 4.2%, 95% confidence interval (CI): -1.9 to 10.3). As the lower limit of the CI was higher than -12%, raltegravir was judged to be non-inferior to efavirenz (p<0.0001). Again, raltegravir was associated with a more rapid decline in HIV-1 RNA. Virological response to treatment was comparable between treatments irrespective of baseline plasma HIV-RNA, baseline CD4 count or HIV-1 subtype[11].

**5.1.2 Treatment experienced**

BENCHMRK 1 & 2 were identical randomised, double-blind, placebo-controlled trials comparing raltegravir 400mg twice daily (n=462 with placebo (n=237), both with an OBR. Patients had triple-class resistant HIV-1 infection and the majority had a prior diagnosis of AIDS. Around 65% of patients in both studies were sensitive to less than two of the agents in their OBR (and around 20-30% were not sensitive to any agents) based on genotypic sensitivity scores[13,14]. In BENCHMRK 1, where treatment-related discontinuation = failure, the primary endpoint of HIV-1 RNA levels <400 copies/mL at week 16 was achieved in 78.4% (178/227) of the raltegravir group and 41.0% (48/117) of the placebo group and in BENCHMRK 2, 78.3% (177/226) and 43.2% (51/118), respectively, (p<0.001). HIV-1 RNA levels <50 copies/mL in BENCHMRK 1 were 62.1% (141/227) and 33.3% (39/117) and in BENCHMRK 2 62.8% (142/226) and 36.4% (43/118), (p<0.001), respectively[12].

48-week data[12-14].

The proportion of patients achieving HIV RNA <50 copies/mL in both the raltegravir and the placebo groups was numerically greater in those who had lower HIV RNA levels and higher CD4 cell counts at baseline, and those who had a higher number of agents in their OBR to which their virus was sensitive (as assessed by genotypic or phenotypic sensitivity scores).

First time use of darunavir or enfuvirtide in the OBR was associated with higher response rates in both the raltegravir and placebo groups and accounted for the majority of response in the placebo group.

**5.1.3 Switching studies**

CHEER was an open label historical control study in HIV-1 infected treatment-experienced adults on a stable antiretroviral regimen containing enfuvirtide and at least two other antiretrovirals with a HIV-1 RNA level of ≤50 (depending on assay used) for at least six months. Patients were switched from enfuvirtide 90mg given subcutaneously (SC) twice daily to raltegravir 400mg given orally twice daily, the background antiretrovirals remained unchanged. The primary outcome was the proportion of patients who maintained a HIV-1 RNA level below 50 or 75 copies/mL at 24 weeks and was met by 49 of the 52 patients who received treatment. Patient treatment satisfaction scores were also significantly improved at 12 weeks[15].

EASIER was a prospective open-label trial in multidrug resistant adults with HIV-1 infection and plasma levels < 400 copies/mL who were receiving enfuvirtide-based regimens. Patients (n=169) were randomised to remain on enfuvirtide 90mg given SC twice daily or switched to raltegravir 400mg given orally twice daily. The primary endpoint of virological failure rate (HIV-1 RNA ≥400 copies/mL) over 24 weeks was 1.2% in both treatment arms. The treatment difference was 0.01% (95% CI: -6.7 to 6.8%; p<0.002); raltegravir was judged to be non-inferior to enfuvirtide as the upper limit of the 95% CI was ≤10%[16].

SWITCHMRK 1 & 2 were identical double-blind, randomised, active-controlled studies in patients on a stable lopinavir/rotinavir regimen in combination with at least two NRTIs (and no other active PI) who had not received any lipid lowering therapy for at least three months. Patients had HIV-1 RNA levels <50 copies/mL and were not required to be intolerant of lopinavir/ritonavir. Patients were randomised to remain on lopinavir/ritonavir (400mg/100mg twice daily) (n=352) or be switched to raltegravir 400mg twice daily (n=350). The primary clinical endpoints were the change in serum lipid concentrations from baseline to week 12 and the proportion of patients with HIV-1 RNA levels <50 copies/mL at week 24 with an inferiority margin of -12% for each study (non-completer = failure). The percentage change in lipid parameters was significantly greater for raltegravir (p<0.001): total cholesterol was -12.6% versus 1.0%, non-HDL cholesterol -15.0% versus 2.6% and triglycerides -42.4% versus 6.2% for raltegravir and lopinavir/ritonavir treatment groups, respectively. However both studies were terminated at week 24 due to lower than expected virological response rates with raltegravir (treatment difference -6.2%, 95% CI: -11.2 to -1.3)[17].

**5.2 Safety**

In the STARTMRK study the safety profile of raltegravir was comparable to efavirenz when both agents were used in combination with Truvada® in treatment naïve adults[11]. The Committee of Medicinal Products for Human Use (CHMP) state that efavirenz was associated with higher incidences of rashes and adverse effects of the nervous system when compared to raltegravir[18]. The mean change from baseline in lipid profile was significantly lower in the raltegravir versus the efavirenz group. However the difference between the changes in total cholesterol/HDL-cholesterol was not significant[11]. Elevation in bilirubin occurred more frequently in the raltegravir group; this was generally mild in nature and usually spontaneously resolved[18]. Due to these effects on bilirubin, changes were made to the SPC noting that raltegravir is an inhibitor of UGT1A1; though the likelihood of a clinically significant drug interaction due to inhibition of raltegravir through this mechanism appears to be low[1]. The solubility of raltegravir increases with increasing pH[16]. Data from the trials indicates that adverse effects were more common in those patients on concomitant acid suppressants, though the number of patients on acid suppressants was low (19/281)[18]. Based on prior data from healthy subjects, the SPC already cautions the use of raltegravir in combination with proton pump inhibitors and histamine-2 antagonists[1].

In the EASIER trial, although overall incidence of adverse reactions was comparable, more patients experienced raised liver enzymes and increases from baseline in triglyceride and total cholesterol following a switch to raltegravir. Two patients on raltegravir, both of whom were on a tipranavir-containing regimen, had to discontinue treatment due to grade 4 increases in alanine transferase[16]. CHEER performed a sub-group analysis on those patients receiving a background of tipranavir/ritonavir and found an increased rate of modest liver enzyme elevations compared with patients not on this background regimen[15], although patient numbers were small and therefore this should be viewed with caution.

## 6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The SWITCHMRK study assessed switching from a lopinavir/ritonavir containing regimen in patients who had undetectable viral loads to a raltegravir containing regimen. Despite improvements in lipid markers the study failed to meet the criteria for virological non-inferiority[17]. BHIVA suggest that this may have been due to pre-existing resistance in the backbone relating to previous treatment. They reinforce that care is taken when switching patients from a boosted PI (due to intolerance) to raltegravir and that raltegravir should be used with a backbone containing other active agents in multiple treatment experienced patients[7].
- The SPC states that as raltegravir has a relatively low genetic barrier to resistance, whenever possible, it should be administered with two other active antiretrovirals to minimise the potential for virological failure and the development of resistance[1].
- The CHEER and EASIER study both found raltegravir to be non-inferior to enfuvirtide when switching virologically suppressed patients from enfuvirtide[15,16]. However treatment numbers were comparatively low to those in SWITCHMRK[17].
- In treatment naïve patients, raltegravir was used in combination with tenofovir and emtrictabine (Truvada®)[11] or tenofovir and lamivudine[9,10], there are no data on the use of raltegravir in combination with other antiretrovirals e.g. PIs in this patient population.
- None of the studies have been specifically designed to assess the efficacy of raltegravir in patients who are unable to receive other antiretrovirals due to specific drug-drug interactions or significant co-morbidities.
- No dose adjustments are required when raltegravir is co-administered with tenofovir, tipranavir/ritonavir, atazanavir/ritonavir, etravirine or maraviroc[1]. Raltegravir is not altered and does not affect CYP450 or the P-glycoprotein system, therefore interactions with products that affect or a substrate for CYP450 or P-glycoprotein are not expected[1]. This may be of benefit in patients on multiple drug therapy.

## 7.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

### 7.1 Cost-effectiveness evidence

#### 7.1.1 Context

A simple CMA has been conducted to compare raltegravir against enfuvirtide in a select group of patients described by the company as those who are intolerant or resistant to NNRTIs or PIs or for whom these options are compromised due to drug-drug interactions[2]. No evidence on the cost effectiveness of raltegravir in treatment-naïve patients is provided, nor in treatment-experienced patients who are candidates for other agents.

The choice of the comparator is reportedly based on the licensed indications for raltegravir[1] and enfuvirtide[6], which the company considers are the only agents licensed for use in patients who have intolerance to previous antiretroviral therapies[2]. Maraviroc is excluded as a comparator due to its restriction for use only in treatment-experienced patients who are infected with CCR5-tropic HIV-1[19]. The assumption of comparable efficacy of raltegravir and enfuvirtide is based on 24-week data from a prospective observational study (CHEER)[15] and a randomised open-label study (EASIER)[16], both of

which were conducted in patients who were already stabilised on enfuvirtide and were switched to raltegravir. Details of the methods employed are presented in Appendix 2.

### 7.1.2 Results

The CMA considers only drug acquisition costs, which are lower for raltegravir compared with enfuvirtide (see Table 1). On the assumption of equivalence in all dimensions of health outcomes, the company considers this to demonstrate that raltegravir is a cost effective treatment option in this patient population[2].

**Table 1. Company-reported drug acquisition costs for raltegravir and enfuvirtide[2]**

| | Raltegravir* | Enfuvirtide | Difference |
|---|---|---|---|
| Daily cost | £20.54 | £36.78 | -£16.24 |
| Annual cost | £7,497.34 | £13,424.70 | -£5,927.60 |
| *Current BNF list price is £21.58/day[20], but the Company has confirmed above new price is effective from 1st Jan 2010. | | | |

### 7.1.3 WMP Critique

Limitations of the economic evidence:

- The CMA approach assumes that raltegravir and enfuvirtide are equivalent in all dimensions of health outcome over a patient's lifetime, including effectiveness (e.g. survival), safety, tolerability, health-related quality of life and patient preferences. Only short term data are available to lend support to the non-inferiority of raltegravir compared with enfuvirtide in terms of virological and immunological response.
- The EASIER randomised trial found a higher incidence of grade 1–4 laboratory abnormalities in the raltegravir arm (71%), compared with the enfuvirtide arm (46%; P=0.001) and median increases from baseline in triglyceride and total cholesterol levels were significantly higher in the raltegravir arm compared with the enfuvirtide arm. The assumption of equivalence in terms of adverse events is therefore debatable.
- The CMA approach precludes consideration of potential differences in patient preferences related to routes of administration of raltegravir (twice daily oral administration) and enfuvirtide (twice daily subcutaneous injection).
- Although raltegravir is now licensed for treating a broad population of treatment-experienced and treatment-naïve patients, the economic data provided by the company are limited to a specific sub-population and does not inform its cost effectiveness in treatment-naïve patients. The company anticipates that raltegravir will only be used when toxicity, drug interactions or resistance would prevent an effective regimen of three BHIVA-recommended agents, and will not replace existing therapies when these are effective and well tolerated[2].

## 8.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

### 8.1 Budget impact evidence

#### 8.1.1 Context

The budget impact analysis relates to the use of raltegravir in treatment-experienced patients who would otherwise use enfuvirtide due to tolerability or resistance to other established therapies. Estimation of the number of patients likely to be prescribed raltegravir due to these factors is complex, and the budget impact analysis is largely based on company-sought expert opinion.

#### 8.1.2 Methods

Based on company-sought expert opinion it is estimated that around 20 patients on triple therapy would be eligible for treatment with raltegravir on tolerability grounds in the first year. Thereafter, the number of patients is anticipated to increase by 15% each year, based on the mean average annual increase in the number of patients accessing HIV care between 2000 and 2008. It is assumed that most patients would remain on treatment for at least five years, such that those starting treatment in 2010 would still receive treatment in 2014[2]. Only drug acquisition costs are considered in the analysis (see Table 2 in section 8.13). The net budget impact estimates assume 100% uptake of raltegravir.

#### 8.1.3 Results

**Table 2. Company estimates of cost savings with raltegravir treatment instead of enfuvirtide[2]**

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| No. of patients | 20 | 23 | 26 | 30 | 35 |
| Cost/year with raltegravir treatment | £149,942 | £172,433 | £194,925 | £224,913 | £262,399 |
| Cost/year with enfuvirtide treatment | £268,494 | £308,768 | £349,042 | £402,741 | £469,865 |
| **Cost savings with raltegravir** | **-£118,552** | **-£136,335** | **-£154,118** | **-£177,828** | **-£207,466** |

#### 8.1.4 WMP Critique

The company has taken a pragmatic approach to estimate the number of patients likely to be eligible for treatment with raltegravir under the present scenario of use. These are informed by company-sought expert opinion and the assumption of a constant increase in patient numbers based on historical data. However, such estimates and assumptions are subject to a degree of uncertainty.

### 8.2 Comparative unit costs

Under the scenario of use presented by the company, enfuvirtide is the comparator, and unit costs are presented in Table 1, section 7. Raltegravir is licensed in a broad HIV patient population and there is a wide range of regimens that may be possible, depending on individual patient factors, treatment histories and resistance profiles. It is not possible to derive comparative unit costs for all potential comparators.

## 9.0 ADDITIONAL INFORMATION

### 9.1 Shared care arrangements

Raltegravir should be initiated by specialists and would not currently be deemed suitable for shared care.

### 9.2 Previous AWMSG advice

AWMSG has appraised a number of antiretroviral medicines for the treatment of HIV-1 infection, the recommendations can be viewed via the 'Appraisal Recommendations' page on the AWMSG website www.wales.nhs.uk/awmsg.

### 9.3 Ongoing studies

Studies PN004, STARTMARK and BENCHMRK are ongoing. 144-week data for BENCHMRK is due imminently and 144-week STARTMRK data are expected in the next six months[2].

### 9.4 Patient Organisation Information

A patient organisation submission by The Terrence Higgins Trust was provided

### 9.5 Medical expert/Clinical expert summary

A summary of medical/clinical expert views was provided

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## Appendix 1. Additional Clinical Information

### Table 1A. Treatment naïve adults

| Ref | Study type | No. patients | Inclusion criteria | Baseline characteristics | Treatment regimens | End points (Raltegravir versus efavirenz) |
|---|---|---|---|---|---|---|
| STARTMRK [11,18] | DB, R, PIII, non-inferiority study.<br>48 weeks with extension to 96 weeks (data not provided) & ongoing | 563 | ≥18yrs<br><br>HIV RNA >5000 copies/mL<br><br>No prior ART | 81% male<br>43% Caucasian<br>80% Clade B<br>48% CD4 ≤200 cells/microL<br>27% HIV RNA ≤50,000 copies/mL<br>6% HepB/C | RAL 400mg bd plus TDF/FTC<br><br>or<br><br>EFV 600mg od plus TDF/FTC | **Primary endpoint (48 weeks):**<br>Proportion of patients achieving HIV RNA <50 copies/mL: 86.1% vs. 81.9% (group difference 4.2% [95% CI: -1.9 to 10.3]; p<0.001). Non-inferiority met.<br><br>**Secondary endpoints (48 weeks):**<br>Proportion of patients achieving HIV RNA <400 copies/mL: 90.0% vs 85.8% (group difference 4.1% [95% CI: -1.28 to 9.68]; p<0.001). Non-inferiority met.<br>Change from baseline in CD4 cell counts (cells/$mm^3$): 189 vs 163 (mean difference 26 [95% CI: 4 to 47]) |
| PN004 [9,10] | DB, R, dose ranging study<br><br>48 weeks with extension to 144 weeks (ongoing)<br><br>Not powered for formal efficacy comparisons between RAL & EFV. | 198 | ≥18yrs<br><br>Susceptible to EFV, TDF, 3TC<br><br>No prior ART<br><br>HIV RNA ≥ 5000 copies/mL<br><br>CD4 ≥ 100 cells/$mm^3$ | 79% male<br><br>31% Caucasian<br><br>55% HIV RNA >50,000 copies/mL<br><br>CD4-mean (cells/$mm^3$): RAL = 305; EFV = 280<br><br>HIV RNA copies/ml** ($log_{10}$ copies/mL): RAL = 55266 (4.8) EFV = 67554 (4.8) | RAL 100, 200, 400 or 600mg bd (to 48 weeks) then 400mg bd plus TDF/FTC<br><br>or<br><br>EFV 600mg od plus TDF/FTC | **Endpoints (24 weeks):**<br>Proportion of patients achieving HIV RNA <400 copies/mL: 85-98% (all groups) vs 95%<br>Proportion of patients achieving HIV RNA <50 copies/mL: 85-95% (all groups) vs 92%<br>Change from baseline in CD4 cell counts (cells/$mm^3$): 128-175 vs 109<br>**Endpoints (48 weeks):**<br>Proportion of patients achieving HIV RNA <400 copies/mL: 92.5 vs 86.8% (difference 5.7 [95% CI: -3.4 to 20.3])<br>Proportion of patients achieving HIV RNA <50 copies/mL: 85.6 vs 86.8% (difference -1.2 [95% CI: -11.2 to 13.7])<br>Change from baseline in CD4 cell counts (cells/$mm^3$): 174 vs 170 (difference 4 [95% CI:-45 to 54])<br>**Endpoints (96 weeks):**<br>Proportion of patients achieving HIV RNA <400 copies/mL: 84.4 vs 84.2 (difference 0.2 [95% CI: -10.6 to 15.6])<br>Proportion of patients achieving HIV RNA <50 copies/mL: 83.1% vs 84.2% (difference -1.1 [95% CI: -12.0 to 14.5])<br>Change from baseline in CD4 cell counts (cells/$mm^3$): 221 vs 232 (difference -11 [95% CI: -69 to 47]) |

**Table 1B. Treatment experienced adults**

| Ref | Study type | No. patients | Inclusion criteria | Baseline characteristics | Treatment regimens | End points (Raltegravir versus placebo) |
|---|---|---|---|---|---|---|
| BENCHMRK 1 & 2[2,12-14] | DB, PIII, RCTs<br><br>48 weeks (extension to 152 weeks)<br><br>Combined results | 699 | ≥16 yrs<br><br>Resistance to ≥1 drug in each of 3 classes (NNRTI plus NRTI plus PI)<br><br>HIV RNA >1000 copies/mL | 88% male<br><br>67.7% Caucasian<br><br>Mean age 46yrs<br><br>Mean CD4 count 155 cells/$mm^3$<br><br>Mean HIV RNA ($log_{10}$ copies/mL) 4.6<br><br>92% prior history of AIDS<br><br>Previous ART: median 12 drugs over median 10 yrs<br><br>16% Hep B and/or C co-infection. | RAL 400mg bd vs placebo | **Primary endpoint (16 weeks):** (TD=F)<br>Proportion of patients achieving HIV RNA <400 copies/mL:<br>BENCHMRK 1: 78.4% (178/227) vs. 41.0% (48/117); p<0.001<br>BENCHMRK 2: 78.3% (177/226) vs. 43.2% (51/118); p<0.001<br><br>**Secondary endpoints (16 weeks):** (TD=F)<br>Proportion of patients achieving HIV RNA <50 copies/mL:<br>BENCHMRK 1: 62.1% (141/227) vs. 33.3% (39/117) ; p<0.001<br>BENCHMRK 2: 62.8% (142/226) vs. 36.4% (43/118); p<0.001<br><br>**Secondary endpoints (48 weeks)**: (NC=F)<br>Proportion of patients achieving HIV RNA <400 copies/mL:<br>72.3% vs 37.1% (p<0.001)<br>Proportion of patients achieving HIV RNA <50 copies/mL:<br>62.1% vs 32.9% (p<0.001)<br>Change from baseline in CD4 cell counts (cells/$mm^3$): 109 vs 45 (p<0.001)<br><br>**Other endpoints (96 weeks)[2]**:<br>Proportion of patients achieving HIV RNA <400 copies/mL:<br>62% vs 28% (p<0.001)<br>Proportion of patients achieving HIV RNA <50 copies/mL:<br>57% vs 26% (p<0.001) (NC=F)<br>Change from baseline in CD4 cell counts (cells/$mm^3$): 123 vs 49 (p<0.001) (OF) |

3TC: lamivudine, ART: antiretroviral therapy, ARV:antiretroviral, bd: twice daily, CI: confidence interval, DB: double blind, EFV: efavirenz, ENF: enfuvirtide, HDL: high density lipoprotein, Hep B: hepatitis B, Hep C: hepatitis C, LDL: low density lipoprotein, LPVr: Kaletra, NC=F: NNRTI: non-nucleoside reverse transcriptase inhibitor, non-completer = failure, NRTI: nucleoside reverse transcriptase inhibitor, NS: not significant, OBT: Optimised background therapy, od: once daily, OF: observed failure, OL: open-label, PCR: polymerase chain reaction, PI: protease inhibitor, R: randomised, RAL: raltegravir, RCT: randomised controlled trial, RNA: ribonucleic acid, TD=F: treatment-related discontinuation = failure, TDF/FTC: tenofovir/emtricitabine (Truvada), vs: versus
**geometric mean

**Table 1C. Switch Studies (Treatment-Experienced)**

| Ref | Study type | No. patients | Inclusion criteria | Baseline characteristics | Treatment regimens | End points |
|---|---|---|---|---|---|---|
| CHEER[15] | OL, historical control, switch study<br><br>24 weeks | 52 | ≥ 18yrs<br><br>On a stable ARV regimen consisting of ENF SC + 2 ARVs<br><br>HIV RNA <75 copies/mL by bDNA assay or <50 copies/mL by ultrasensitive PCR assay for ≥6 months | 92% male<br><br>Mean age 53 yrs<br><br>Baseline CD4 count 377 cells/mm$^3$<br><br>Previous ART: mean 15 drugs over 15 mean yrs | RAL 400mg bd plus OBT | **Primary endpoint (24 weeks):**<br>Proportion of patients who maintained a level of HIV RNA below the limit of quantification of the assay used: 94.2%<br><br>**Secondary endpoints (24 weeks):**<br>Change from baseline in CD4 cell counts (cells/mm$^3$): 32 (range -165 to 323)<br>Impact of regimen change on quality of life as assessed by changes in scores in patient treatment satisfaction surveys administered at baseline, week 12 and week 24: Week 0 to 12: p<0.0001 & Week 12 to 24: NS |
| EASIER[16] | R, OL study<br><br>24 weeks with extension to 48 weeks | 169 | Triple class failure or intolerance<br><br>Integrase inhibitor-naïve<br><br>HIV RNA < 400 copies/mL for >3 months | 85% male<br>Median age 48 yrs<br>Median CD4 cell count (cells/mm$^3$): RAL= 410 & ENF= 374<br>HIV RNA <50 copies/mL: RAL= 85% & ENF= 88%<br>Median duration of ENF 2.4yrs | RAL 400mg bd, plus OBT<br><br>or<br><br>ENF 90 mg SC bd plus OBT | **Primary endpoint (24 weeks): RAL vs ENF**<br>Cumulative proportion of patients with virologic failure (HIV RNA ≥ 400 copies/mL: 1.2% vs 1.2% (difference 0.01% [95% CI: -6.7 to 6.8]; p<0.002). Non-inferiority met.<br><br>**Secondary endpoints (24 weeks): RAL vs ENF**<br>Proportion of patients with a plasma HIV RNA level <50 copies/mL: 88% vs 88%; p=0.81 (NS)<br>Median increase from baseline in CD4 cell counts (cells/mm$^3$): 11 vs 15; p=0.31 (NS)<br>Proportion of patients experiencing AIDS-defining event or death: none |
| SWITCHMRK 1 & 2[2,17] | DB, PIII, RCTs<br><br>24 weeks | 702 | ≥ 18yrs<br><br>HIV RNA <75 copies/mL or <50 copies/mL<br><br>Virologically suppressed, stable LPVr plus 2NRTIs regimen for ≥ 3 months | Approx: 78% male<br><br>Mean age 43 yrs<br><br>65% Caucasian<br><br>Mean CD4 count (cells/mm$^3$): 485<br><br>95% HIV RNA <50 copies/mL | RAL 400mg bd plus 2 NRTIs<br><br>or<br><br>LPVr 250mg bd plus 2 NRTIs | **Primary endpoint: RAL vs LPVr**<br>Mean % change in lipids at week 12: SWITCHMRK 1: Fasting cholesterol: -13% vs 1%; p<0.001, fasting triglycerides -41% vs 4%; p<0.001, non-HDL-C -15% vs 2%; p<0.001, fasting LDL-C -2% vs 2%, p=0.704.<br>SWITCHMRK 2: Fasting cholesterol: -12% vs 1%; p<0.001, fasting triglycerides -43% vs 8%; p<0.001, non-HDL-C -15% vs 3%; p<0.001, fasting LDL-C 4% vs 1%, p=0.269<br>Proportion of patients with a plasma HIV RNA level <50 copies/mL (NC=F):<br>SWITCHMRK 1: 81% vs 87% (difference -6.6 [95% CI:-14.4 to 1.2])<br>SWITCHMRK 2: 88% vs 94% (difference -5.8 [95% CI:-12.2 to 0.2])<br>Not met non-inferiority margin of 12%. |

## Appendix 2. Additional Health Economic Information[2]

| Base Case Model | | Appropriate? |
|---|---|---|
| **Comparator(s)** | Raltegravir compared against enfuvirtide | Evidence restricted to comparison of raltegravir against enfuvirtide in a select group of patients. Precludes a comparison against any other agents. |
| **Population and setting** | Patients described by the company as those who are intolerant or resistant to NNRTIs or PIs or for whom these options are compromised due to drug-drug interactions. | No evidence on the cost effectiveness of raltegravir in treatment-naïve patients is provided, nor in treatment experienced patients who are candidates for boosted PI treatment. |
| **Model type and description** | Simple cost minimisation analysis (CMA) | CMA requires that the comparators are equivalent in all dimensions of health outcome. The basis of the assumption of equivalence is very limited (see below). |
| **Perspective** | Considers direct medical costs only, from perspective of NHS Wales | Yes |
| **Time Horizon** | One year | Patients with HIV are expected to survive for longer than 1 year, and treatment is life-long. Although outcomes are assumed to be the same, cost differences will exist over the longer term. |
| **Discount rate** | Not applicable due to one year time horizon | Yes, given the company's choice of a 1-year analytic time horizon |
| **Efficacy** | An assumption of equivalence for raltegravir and enfuvirtide is made based on 24-week data from a prospective observational, historical control study (CHEER, n=52)[15] and a randomised, open-label trial (EASIER, n=170)[16], both conducted in patients who had multi-drug resistant HIV-1 and were stabilised on enfuvirtide. | Both studies concluded that switching to raltegravir was non-inferior to maintaining enfuvirtide in terms of maintaining virological response (HIV RNA <400 and <50 copies/ml) at 24 weeks. These data support a claim of non-inferiority in terms of short term virological (and immunological) response. However, longer term data of health outcomes are required to confirm equivalence. |
| **Adverse effects** | Not included | It is implicitly assumed that adverse event rates are equivalent. The CHEER observational study is unable to support this assumption due to a lack of a comparator arm. The EASIER randomised trial found a higher incidence of patients who experienced grade 1–4 laboratory abnormalities in the raltegravir arm (71%), compared with the enfuvirtide arm (46%; P=0.001), related to a higher incidence of neutropenia (11% vs. 2%) and increased LFTs in the raltegravir arm versus the enfuvirtide arm. The median increases from baseline in triglyceride and total cholesterol levels were significantly higher in the raltegravir arm, compared with the enfuvirtide arm. These are based on short term data, and it is uncertain that there would be no additional resource use associated with management of adverse events in the longer term. |
| **Utility values** | Not included | Only appropriate if the assumption of equivalence holds. CMA precludes consideration of patient s' preferences for oral treatment compared with parenteral treatment. |
| **Resource use and costs** | Relate only to drug acquisition costs | Only appropriate if the assumption of equivalence holds. |
| **Model Provided?** | N/A | N/A |
| **Other considerations** | N/A | N/A |