# raltegravir, 400mg film-coated tablet (Isentress) No. (461/08)

## Merck, Sharp and Dohme Limited

04 April 2008

The Scottish Medicines Consortium 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

**raltegravir (Isentress®)** is accepted for restricted use within NHS Scotland in combination with other antiretroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV-1) infection in treatment experienced adult patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. It is restricted to patients with triple class resistant HIV-1 infection.

Addition of raltegravir to optimised background therapy in treatment experienced patients with documented resistance to at least one drug in each of the three HIV antiviral classes, significantly increased the number of patients achieving clinically significant reductions in viral load.

Overleaf is the detailed advice on this product.

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

## Indication

In combination with other antiretroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV-1) infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

## Dosing information

400mg twice daily with or without food. Tablets should not be chewed, crushed or split.

## Product availability date

January 2008

## Summary of evidence on comparative efficacy

Raltegravir is a new class of antiviral agent, a strand transfer inhibitor of HIV integrase. Incorporation of viral genetic material into the human deoxyribonucleic acid (DNA) is an essential step in the life cycle of HIV-1. The HIV encoded enzyme, integrase, which has no human analogue, catalyses the insertion of the HIV DNA into the host cell genome. This integration provides stable maintenance of the viral genome and efficient viral gene expression and replication.

Two identical, phase lll, randomised, placebo-controlled studies treated a total of 699 treatment-experienced adult patients with raltegravir 400mg twice daily or placebo in combination with optimised background therapy (OBT). Patients included had been treated with stable antiretroviral therapy (ART) for at least 2 months, had documented genotypic/ phenotypic resistance to at least one drug in each of the three classes (non-nucleotide reverse transcriptase inhibitors (NNRTIs), nucleotide reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs)), had a viral load of HIV RNA > 1000 copies/ml and could be co-infected with hepatitis B and/or C. Patients were randomised in a 2:1 ratio with stratification for degree of resistance to PI (one PI vs > one PI) and use of enfuvirtide in the OBT. Prior to randomisation, the investigator selected the OBT for each patient.

The primary analysis population was the modified intention to treat (mITT); all patients who received any study medication. The primary endpoint was the percentage of patients who had a viral load of HIV RNA < 400 copies/ml at 16 weeks with further assessment from the percentage of patients with HIV RNA < 50 copies/ml, a more stringent test and the optimal outcome. The CD4 cell count change from baseline and the HIV RNA change from baseline at 16 weeks were further markers of treatment response. These endpoints were also assessed at 24 weeks. Patients virologically failing at or after week 16 were considered as failures and could receive open-label raltegravir.

At week 16, raltegravir was significantly superior to placebo in both studies, based on a logistic regression model adjusted for baseline HIV RNA level, enfuvirtide use in OBT and active PI in OBT. The model adjusted odds ratios (95% confidence interval (CI)) for this primary endpoint between raltegravir and placebo, were 10.6 (5.60 to 20.25) and 9.6 (5.02 to 18.25) for studies 1 and 2, respectively. The percentages of patients with HIV RNA < 400 and < 50 copies/ml for raltegravir versus placebo were 77% vs 41% and 61% vs 33% for study 1 respectively, and 77% vs 43% and 62% vs 36% for study 2 respectively. At week 16, 7% (33/462) of raltegravir patients and 36% (85/237) of placebo patients were treatment failures and were assigned to open-label raltegravir.

Week 24 outcomes were similar to the 16 week results and demonstrated a sustained response. (Table1).

**Table 1. Key primary and secondary outcomes at Week 24 using pooled data from the two pivotal Phase III studies.**

| Outcome at week 24 | Raltegravir 400 mg bd (n = 462) | Placebo (n = 237) |
|---|---|---|
| Patients with HIV RNA < 400 copies/ml, n (%) | 347 (75) | 95 (40) |
| Patients with HIV RNA < 50 copies/ml, n (%) | 289 (63) | 80 (34) |
| Mean change from baseline in HIV RNA ($log_{10}$copies/ml) | -1.82 | -0.87 |
| Mean change from baseline in CD4 cell count (cells/$mm^3$) | 84 | 37 |
| Virologic Failure (confirmed), n (%) | 84 (18) | 127 (54) |
| Discontinuations for any reason, n (%) | 16 (3) | 7 (3) |

n=number, bd=twice daily

## Summary of evidence on comparative safety

In the two pivotal phase lll studies, the adverse event profile of raltegravir was similar to that of placebo with most events mild to moderate. Refer to the summary of product characteristics for details. Comparative safety data for raltegravir are only available with efavirenz in treatment-naive patients. Raltegravir did not significantly raise triglycerides, total cholesterol or LDL-cholesterol compared with efavirenz and produced significantly fewer drug-related adverse events. There is a lack of long-term data for raltegravir and monitoring is to continue after marketing.

## Summary of clinical effectiveness issues

Raltegravir has a novel mechanism of action and therefore may be an option in those patients who are resistant to all other classes of antiretroviral. It is metabolised mainly by glucuronidation and should not interact with other HIV therapies.

There is a low genetic barrier to the selection of raltegravir-resistant mutants and further evaluation is needed as analysis of resistance is based on only 41 treatment failures. The clinical importance of intermittent or persistent low plasma exposure to raltegravir in terms of the risk of selecting for drug-resistant virus and virological failure has not been fully established. Adherence is an important factor in the development of resistance to drug therapy, however, information on adherence to therapy was not reported in the pivotal studies.

The European Medicines Agency (EMEA) noted no major safety concerns in the clinical trial programme. However longer-term safety data are required to confirm some specific safety issues and these have been included in the post-marketing Risk Management Plan.

## Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis of raltegravir plus optimised background therapy (OBT) relative to OBT alone over a thirty year time horizon. This employed a cohort state-transition modelling approach, within a continuous time framework. Patient health states were defined in terms of HIV-RNA viral loads and CD4 cell counts. Patients could also experience a range of opportunistic infections, the likelihood of these being related to CD4 cell counts.

An additional analysis was presented for raltegravir displacing darunavir within OBT, rather than being additional to OBT. A similar analysis was presented for enfuvirtide. Subgroup analysis of the clinical trials to exclude darunavir or enfuvirtide patients from the raltegravir arm and only include darunavir or enfuvirtide patients within the OBT arm was used as the basis of these additional analyses.

For the transitions between HIV-RNA viral load states the clinical trials were the main data source. They were also the data source for the transitions between CD4 cell count states, these also being differentiated by HIV-RNA viral load state and by treatment arm. The likelihood of developing an opportunistic infection, and the effects of this, were derived from the literature. Quality of life values were taken from the literature, though the source adjusted these to remove side-effects of ritonavir. Ongoing resource use not related to drug costs or opportunistic infections was estimated through expert opinion.

The manufacturer estimated raltegravir would yield an additional 1.7 QALYs at an additional cost of £39,274 compared to OBT. This resulted in a cost-effectiveness estimate of £23,418 per QALY. In the comparison with darunavir, raltegravir was estimated to be more expensive but superior to darunavir with a cost-effectiveness estimate of £33,142 per QALY from lifetime raltegravir use. In the comparison with enfuvirtide, raltegravir was estimated to dominate, being both cheaper and more effective.

There were some concerns with the analysis. Some of the assumptions regarding the flows of patients in the first five years of the model may have introduced some bias in favour of raltegravir. The result also showed some sensitivity to the inclusion of quality of life adjustments for opportunistic infections.

Overall, however, the health economic case for use was made.

## Summary of patient and public involvement

Patient Interest Group Submission: HIV Scotland

## Additional information: guidelines and protocols

The British HIV Association (BHIVA), guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006) state that key considerations in the choice of HIV therapy for treatment-experienced patients include treatment history, co-morbid conditions, tolerability, adherence, drug-drug interactions and resistance testing.

## Additional information: previous SMC advice

After review of a full submission the Scottish Medicines Consortium (SMC) issued advice on 4th May 2007 that darunavir (Prezista®) is accepted for use within NHS Scotland, co-administered with ritonavir and in combination with other antiretroviral medicinal products, for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who have failed on more than one regimen containing a protease inhibitor (PI). At 24 and 48 weeks, darunavir, in combination with low dose ritonavir, showed a significant improvement in the reduction of viral load compared with other protease inhibitor plus ritonavir regimens.

After review of a full submission the Scottish Medicines Consortium (SMC) issued advice on 11th August 2003 that enfuvirtide (Fuzeon®) is recommended for restricted use within NHS Scotland. Restricted to use by clinicians experienced in the management of HIV infected patients. It is licensed for use in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected patients who have received treatment with and failed on regimens containing at least one medicinal product from each of the following antiretroviral classes, protease inhibitors, non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors, or who have intolerance to previous antiretroviral regimens.

## Additional information: comparators

No other members of this class are currently licensed, and raltegravir is added to background therapy, therefore there are no direct comparators. However, in sub-analysis in the economics, enfuvirtide and darunavir, have been used as comparators.

## Cost of relevant comparators

| Drug | Dose regimen | Cost per year (£) |
|---|---|---|
| **Raltegravir** | **400mg twice daily** | **7,855** |
| Enfuvirtide | 90mg sc twice daily | 13,931 |
| Darunavir + ritonavir | 600mg twice daily + 100mg twice daily | 6,235 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 22nd January 2008.

## Additional information: budget impact

Based upon 30 patients in year 1 rising to 41 patients by year 5, the manufacturer estimated a gross drug cost of £235,041 in year 1, rising to £325,773 by year 5. No net drug cost offset was estimated since raltegravir was assumed to be additional to other therapy. Advice from clinical experts suggests that these patient numbers may be an underestimate, with the likely budget impact increasing as a result.

***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.*

*This assessment is based on data submitted by the applicant company up to and including 14 March 2008.*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*

*The reference below, shaded grey, is additional to information supplied with the submission.*

European Medicines Agency (EMEA). European public assessment report (EPAR) for Raltegravir. www.emea.eu.int