Scottish Medicines Consortium

raltegravir, 400mg film-coated tablet (Isentress®) No.(613/10)
Merck, Sharp and Dohme Limited

09 April 2010

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

raltegravir (Isentress®) is accepted for restricted use within NHS Scotland.

Licensed indication under review: in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.

SMC restriction: to patients who are intolerant or resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) or when these options are compromised due to drug-drug interactions.

Raltegravir has been shown to be non-inferior to efavirenz in combination with tenofovir and emtricitabine in treatment naïve patients.

In two small open-label studies, raltegravir demonstrated maintenance of viral suppression over 24 weeks when substituted for enfuvirtide in a combination regimen in highly pre-treated patients with a history of triple class failure or intolerance.

The health economic case was demonstrated only for a sub-population of patients within the licensed indication.

SMC has previously issued advice for raltegravir in the treatment of HIV infection and this extends the advice to cover a wider patient population.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.

Dosing information

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

Therapy should be initiated by a physician experienced in the management of HIV-1 infection.

Product availability date

Not applicable

Summary of evidence on comparative efficacy

Raltegravir is a strand transfer inhibitor of HIV integrase that has no human analogue. HIV integrase catalyses the insertion of the viral HIV DNA into the host cell genome. This integration provides stable maintenance of the viral genome and efficient viral gene expression and replication.

The Scottish Medicines Consortium (SMC) has previously accepted raltegravir for use in combination with other antiretrovirals (ARTs) in treatment-experienced adults with triple class resistant HIV-1 infection and with evidence of HIV-1 replication despite ongoing ART therapy. The licence has now been extended to support use of raltegravir in a broader HIV-1 population including treatment-naïve patients. The submitting company has requested that SMC now considers the use of this product only in a sub-population of adults with HIV-1 infection covered by the licence, namely patients who are intolerant or resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) or when these options are compromised due to drug-drug interactions.

The manufacturer's positioning of raltegravir in this submission is supported by two studies in which patients with viral suppression on regimens including enfuvirtide were switched from enfuvirtide to raltegravir to assess whether viral suppression was maintained.

Treatment-naive patients

In a 96-week, phase III, double-blind, non-inferiority study, 566 (566 were randomised but three patients did not receive any study drug) treatment-naïve HIV-1 infected patients were randomised to either raltegravir 400 mg twice daily or efavirenz 600 mg once daily both in combination with tenofovir 300mg plus emtricitabine 200mg. Patients were stratified on the basis of HIV RNA concentration (>50,000 versus ≤50,000 copies per mL) and viral hepatitis co-infection status. Patients were excluded if they had acute or decompensated chronic hepatitis but patients with chronic hepatitis were eligible if their serum aminotransferase concentrations were less than five times the upper limit of the normal range. The primary outcome measure was the proportion of patients achieving an HIV RNA < 50 copies/mL at 48 weeks in the modified intention to treat (mITT) population Raltegravir was considered non-inferior to efavirenz if the lower bound of the two-sided 95% confidence interval (CI) for the proportion of patients who responded in the raltegravir group minus the efavirenz group was higher than –12%. In the analysis, with all patients who did not complete the study recorded as failures, the primary outcome was achieved by 86% (n=241/281) in the raltegravir group compared with 82% (n=230/282) in the efavirenz group (difference 4.2%,

95% CI: -1.9 to 10.3), indicating that raltegravir was non-inferior to efavirenz. The primary outcome analysis, where only patients who discontinued due to lack of efficacy were considered failures, confirmed raltegravir as non-inferior, with the proportion of patients achieving <50 copies/mL, 92% (n=241/263) in the raltegravir group and 89% (n=230/258) in the efavirenz group (difference 2.5%, 95% CI:-2.6 to 7.7).

Treatment-experienced patients

In two identical, phase lll, randomised, placebo-controlled studies, a total of 699 treatment-experienced adult patients were treated with raltegravir 400mg twice daily or placebo in combination with optimised background therapy (OBT). At 24 weeks, 63% of patients (299/462) in the raltegravir group achieved a viral load of HIV RNA < 50copies/ml compared with 34% (80/237) in the placebo group. These studies are described in detail in the SMC advice for raltegravir published in May 2008.

Switch from enfuvirtide to raltegravir

In a 48-week, randomised, open-label, non-inferiority study in 169 HIV-infected adults with a history of triple class ART failure or intolerance, who had achieved virological suppression (HIV RNA <400 copies/mL for >3 months) with an enfuvirtide regimen, patients were randomised to either continue on their enfuvirtide (90mg subcutaneous [sc] twice daily) or switch to raltegravir (400mg twice daily) in combination with the same background. There were no CD4 cell count restrictions on patients included in the study but patients on concomitant treatment with rifampacin, rifabutin, phenytoin or phenobarbital were excluded.

The primary outcome was the proportion of patients with virological failure, defined as a confirmed plasma HIV RNA level ≥400copies/mL during 24 weeks of the study in the intention to treat population. Non-inferiority was established if the upper limit of the 95% CI of difference in the proportions between groups was ≤10%. The proportion of patients with virological failure was 1.2% in each group (one patient in each group), with the difference between treatments 0.01% (95% CI: -6.7 to 6.8%; p< 0.002). In an on-treatment analysis, censoring patients who discontinued, the proportion of patients who experienced virological failure was 1.2% and 0% in the raltegravir and enfuvirtide groups respectively; difference between treatments 1.22% (95% CI: -5.6 to 8.1%; p <0.001). Therefore non-inferiority was demonstrated.

In a US based, non-randomised, single arm, open-label historical control study, 52 adult HIV-infected patients on a stable ART regimen consisting of enfuvirtide plus at least two other ARTs, had their enfuvirtide 90mg sc twice daily replaced with raltegravir 400mg twice daily to assess the virological effect. Patients had highly resistant HIV infection with multiple primary mutations. The primary outcome was the percentage of patients at week 24 who maintained a viral load below the level of quantification in the intention to treat population and was achieved by 49 of 52 patients (94.2%).

Patient satisfaction was measured via a brief patient treatment satisfaction survey administered at baseline, week 12 and week 24. There was no statistically significant difference between week 12 and week 24 responses. Comparing baseline with week 24 responses showed that patient satisfaction significantly improved on raltegravir-containing regimens.

Summary of evidence on comparative safety

In the above studies no new adverse events that were not known previously were identified.

In the study in treatment-naïve patients, drug-related adverse events reported in ≥10% of patients were dizziness (6% versus 34%, for raltegravir and efavirenz patients, respectively), headache (9% versus 14%), diarrhoea (15% versus 22%), nausea (14% versus 12%) and abnormal dreams (7% versus 13%). In comparison with efavirenz, raltegravir caused significantly fewer adverse drug reactions in general and significantly fewer CNS drug reactions in particular. It also caused smaller changes in serum LDL-cholesterol, HDL-cholesterol, total cholesterol and triglycerides from baseline.

In the randomised enfuvirtide switch study, there was no difference between groups in the number of patients experiencing grade 1 to 4 adverse events during the 24 weeks (78% versus 80% for enfuvirtide and raltegravir groups, respectively). There was no significant difference in grade 3 or 4 adverse events (8% versus 13%, for enfuvirtide and raltegravir). There were a higher number of patients with grade 1 to 4 laboratory abnormalities in the raltegravir group compared with the enfuvirtide group (71% versus 46%, p=0.001). The median increases from baseline in triglycerides and total cholesterol levels were significantly higher in their raltegravir group compared with the enfuvirtide group.

In both enfuvirtide studies in treatment experienced patients, there were reports of patients with elevated liver function tests when raltegravir was co-administered with a tipranavir-based regimen.

Raltegravir is metabolised primarily by UDP glucuronosyltransferases (UGT1A1), therefore inducers of UGT1A1 (eg rifampicin) and inhibitors (eg atazanavir) may affect plasma concentrations. Caution is required when co-administering these agents.

Summary of clinical effectiveness issues

Raltegravir is at present the only integrase inhibitor on the market although others are in development. It has previously been accepted by SMC for restricted use in treatment experienced patients who are triple class resistant. In this submission it has been shown to be non-inferior to efavirenz in combination with tenofovir and emtricitabine in treatment-naïve patients. In two small, open-label studies, raltegravir substituted for enfuvirtide in an enfuvirtide-based combination regimen in highly pre-treated patients, with prior median duration of enfuvirtide therapy of 2.3 to 2.7 years who had achieved viral suppression for at least three months, demonstrated maintenance of viral suppression with raltegravir over 24 weeks.

The submitting company has requested that raltegravir be considered for use in a sub-population of that covered by the licensed indication, in those patients who are intolerant or resistant to NNRTIs or PIs or when these options are compromised due to drug-drug interactions. This is a similar positioning in the treatment pathway to enfuvirtide. The evidence from the two open-label studies supports the use of raltegravir as an alternative to enfuvirtide although there are limitations to both these studies. One was a single arm historical control study, both were open-label with relatively small patient numbers and a longer follow-up is required to confirm that viral suppression is maintained beyond 24 weeks.

Although patients in these studies had a history of triple class failure or intolerance, they were already well controlled on their present regimen prior to substitution with raltegravir. In

practice, patients would be failing or intolerant to their existing regimen and may respond differently.

Raltegravir has a relatively low genetic barrier to resistance and should be administered with two other active ARTs to minimise the potential for virological failure and the development of resistance.

Raltegravir is an oral therapy and is less expensive than enfuvirtide.

Summary of comparative health economic evidence

The manufacturer presented a simple cost-minimisation analysis comparing raltegravir with enfuvirtide. The submission focused on raltegravir for the treatment of HIV-1 infection in adult patients who are intolerant or resistant to NNRTIs or PIs or when these options are compromised due to drug-drug interactions. A one-year time horizon was used and data to support the assumption of comparable efficacy between raltegravir and enfuvirtide were based on the two open-label switch studies. The analysis included only drug acquisition costs with all other resources assumed to be equivalent between the two treatment groups. Based on drug costs alone the manufacturer estimated that raltegravir would be associated with savings of £5,928 per patient per year compared with enfuvirtide in the population of patients of interest.

The analysis was very simple and assumes there would be no difference between the two treatment arms in terms of drug administration costs or resource use. Raltegravir is administered orally whereas enfuvirtide is administered subcutaneously and as such the exclusion of administration costs is likely to be a conservative assumption. SMC clinical experts have indicated that enfuvirtide is an appropriate comparator given the niche proposed by the manufacturer and that there is already some use of raltegravir in this group of patients in Scotland.

There were some weaknesses with the clinical evidence used to support the assumption of equivalent efficacy. The only data relevant to the niche were two open-label switch studies and the patients in these studies did not strictly reflect the niche proposed by the manufacturer i.e. studies included patients with a history of triple class failure or intolerance and didn't necessarily include patients whose options were compromised due to drug-drug interactions.

Based on drug costs alone raltegravir has a lower drug acquisition cost than enfuvirtide. While the evidence to support comparable efficacy with enfuvirtide in the patient group proposed by the manufacturer has some limitations, the economic case for raltegravir as an alternative to enfuvirtide in patients with a history of triple class failure or intolerance was considered to be demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The BHIVA guidelines (2008) recommend that when treatment-experienced patients with options experience sustained viral load rebound on initial therapy, the physician should construct a new HIV treatment that includes at least two (or preferably three) active agents. The use of an agent from a new drug class is likely to be more effective. There are therefore, no pre-specified treatment regimens and as such it is difficult to identify any specific comparator products.

The guidelines discuss the use of raltegravir in treatment- experienced patients, pathways of resistance and a mention of the phase II/III dose-ranging study of raltegravir in treatment-naïve patients in a comparison with efavirenz.

For treatment naïve patients the guidelines recommend that efavirenz should be considered first-line in all patients. This recommendation is based upon its efficacy, durability, toxicity profile, convenience and cost.

Additional information: comparators

Enfuvirtide

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
raltegravir	**400mg orally twice daily**	**7,497**
enfuvirtide	90mg subcutaneously twice daily	13,388

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 26 January 2010.

Additional information: budget impact

The manufacturer estimated there would be net drug budget savings of £456k in year 1 rising to £663k in year 5 based on 77 patients treated with raltegravir in year 1 and 112 in year 5. 100% market share was assumed. The manufacturer highlighted that these savings are likely to be overestimates as many patients have already been switched from enfuvirtide to raltegravir.

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 ***10 March 2010.***

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. 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.

The undernoted references were supplied with the submission.

Lennox JL, DeJesus E, Lazzarin A et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet 2009; 374: 796-806.

DeCastro N, Braun J, Charreau I et al. Switch from Enfuvirtide to Raltegravir in Virologically Supressed Multidrug-Resistant HIV-1-Infected Patients: A Randomized Open-Label Trial. Clinical Infectious Diseases 2009; 49: 1259-67.

Towner W, Klein D, Kerrigan HL et al. Virologic Outcomes of Changing Enfuvirtide to Raltegravir in HIV-1 Patients Well Controlled on an Enfuvirtide Based Regimen: 24-Week Results of the CHEER Study. J Acquir Immune Defic Syndr 2009; 51: 367-73.