Scottish Medicines Consortium

darunavir, 400mg tablets (Prezista®) No. (566/09)
Tibotec, a division of Janssen-Cilag Ltd

07 August 2009

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

darunavir (Prezista®) co-administered with low dose ritonavir and in combination with other antiretroviral medicinal products is accepted within NHS Scotland for the treatment of human immunodeficiency virus (HIV-1) infection in antiretroviral therapy (ART) naïve adults.

After 48 weeks the combination of darunavir and ritonavir was non-inferior to a standard boosted protease inhibitor regimen in ART naïve adults. The combined regimen was associated with lower incidences of diarrhoea and lipid adverse effects.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Darunavir, co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV−1) infection in antiretroviral therapy (ART) naïve adults.

Dosing information

Darunavir 800mg once daily with ritonavir 100mg once daily and with food.
Therapy should be initiated by a physician experienced in the management of HIV infection.

Product availability date

23 February 2009

Summary of evidence on comparative efficacy

Darunavir is a non-peptidic protease inhibitor (PI) with activity against wild type HIV-1 and multi-drug resistant HIV strains. It binds strongly to HIV protease preventing the formation of mature and infectious new virions. Systemic availability is enhanced by the co-administration of low doses of the CYP3A4 inhibitor, ritonavir.

The evidence to support this licence and submission comes from the 48 and 96-week results of an ongoing 192-week multicentre randomised open-label phase III study to assess the efficacy of darunavir/ritonavir compared with lopinavir/ritonavir in the ART naïve patient population.

The study population consisted of ART-naïve HIV-1 infected adults with baseline viral load HIV-1 RNA ≥5,000 copies/mL. Patients co-infected with chronic hepatitis B or C were included if their condition was clinically stable and did not require treatment during the study period. After screening, 689 patients were randomised equally to 192 weeks treatment with darunavir 800mg plus ritonavir 100mg once daily or with lopinavir 800mg plus ritonavir 200mg total daily dose, taken as one single or two divided doses depending on local regulatory approval and investigator/patient preference. All patients also received a fixed background regimen of tenofovir disoproxil fumarate 300mg daily plus emtricitabine 200mg daily. Patients were stratified by plasma HIV-1 RNA (<100,000, ≥100,000 copies/mL) and CD4 cell count (<200, ≥200 cells/mm^3).

The primary outcome was non-inferiority of darunavir/ritonavir to lopinavir/ritonavir for virological response (defined as the percentage of patients with confirmed viral load HIV-1 RNA <50 copies/mL) by per protocol time to loss of virological response [PP-TLOVR]) at 48 weeks. Non-inferiority would be established if the lower limit of the 95% confidence interval (CI) for the difference in virological response between darunavir/ritonavir and lopinavir/ritonavir in the PP study population, (all randomised patients who had received study medication and not taken disallowed therapy for more than one week), at 48 weeks did not exceed -12%. Secondary outcomes included testing for superiority in the intention to treat (ITT) population if non-inferiority was established, HIV-1 RNA <50 copies/mL at 96 weeks, HIV-1 RNA <400 copies/mL, change in HIV-1 RNA and CD4 cell count from baseline, durability of virological response and evaluation of resistance characteristics.

The mean time since diagnosis of HIV-1 infection for the study population was relatively short at 2.5 years and the majority of patients were not considered to have advanced HIV-1 disease. The mean baseline viral load for all patients was 4.85 $\log_{10}$ copies/mL; two thirds of

patients had baseline HIV-1 RNA <100,000 copies/mL, and the median CD4 count was 225 cells/mm^3. Overall, 13% of patients were co-infected with hepatitis B or C virus at baseline. The discontinuation rates for darunavir/ritonavir and lopinavir/ritonavir at 48 weeks were 12% and 16% respectively, and at 96 weeks were 17% and 23% respectively.

The primary outcome of virological response at 48 weeks was achieved in 84% of darunavir/ritonavir and 78% of lopinavir/ritonavir patients (PP-TLOVR) with an estimated treatment difference of 5.6% (95% CI: -0.1 to 11) and therefore non-inferiority was demonstrated. Superiority of darunavir/ritonavir over lopinavir/ritonavir at 48 weeks was not shown.

In a later analysis at 96 weeks, superiority of darunavir/ritonavir over lopinavir/ritonavir in virological response rate (HIV RNA <50 copies/mL) in the ITT population was demonstrated: 79% versus 71%, respectively, with an estimated treatment difference of 8.3% (95% CI; 1.8 to 14.7). There were no significant differences between treatment groups in the proportions of patients with HIV-1 RNA <400 copies/mL, in viral load reduction from baseline or in change in CD4 cell count from baseline at 48 or 96 weeks.

No development of PI resistance was observed up to 48 weeks. No patient failing therapy in either treatment group developed primary PI resistance-associated mutations up to 96 weeks. Isolates from these virological failures remained fully susceptible to all PIs.

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

Summary of evidence on comparative safety

No new safety concerns for darunavir emerged in the ART naïve population compared with its use in ART experienced patients. In the pivotal study most adverse events (AEs) were mild or moderate in severity. At 48 weeks fewer patients in the darunavir group, compared with the lopinavir group, discontinued treatment due to AEs, 3% versus 7%, respectively or experienced serious AEs, 7% versus 12%, respectively. The incidence of grade 2 to 4 diarrhoea at least possibly related to study treatment was significantly lower in the darunavir group compared to the lopinavir group, 4% versus 10%, respectively. Grade 2 to 4 elevations in triglycerides and cholesterol were observed less frequently in the darunavir group, 3% and 13%, than in the lopinavir group, 11% and 23%.

The 96-week safety and tolerability data were consistent with those reported at 48 weeks, with no substantial changes in the incidence of any AEs.

Summary of clinical effectiveness issues

The 48-week data from the pivotal study demonstrate that the virological response of once daily ritonavir-boosted darunavir is non-inferior to that of twice-daily ritonavir-boosted lopinavir in ART naïve patients when both are used in combination with a fixed background regimen of tenofovir and emtricitabine. Superiority of darunavir over lopinavir treatment was not demonstrated at 48 weeks but was shown by 96 weeks.

Darunavir has not been directly compared to the only other PI administered once daily, atazanavir. Once-daily ritonavir-boosted atazanavir was shown to be non-inferior in terms of efficacy to twice-daily ritonavir-boosted lopinavir (both in combination with once-daily tenofovir/emtricitabine) for the initial treatment of ART naïve HIV-1-infected patients over 48 weeks in a patient population similar to that of the pivotal study. Both darunavir and atazanavir, in combination with ritonavir, had lower incidences of gastrointestinal and lipid toxicity than lopinavir/ritonavir. Darunavir has not been shown to cause the hyperbilirubinaemia observed with atazanavir treatment.

A limitation of the pivotal study is that patients were permitted to use once or twice daily dose regimens of lopinavir/ritonavir. Fifteen percent of the study population received the once daily regimen and a further 8% switched between once and twice daily dosing during the study. The once daily regimen is not licensed in the European Union.

Although the pivotal study found that significantly more patients with high baseline viral load, and numerically more patients with low baseline CD4 cell count, responded to darunavir/ritonavir than to lopinavir/ritonavir, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency questioned whether the study was sufficiently robust to claim a clinical benefit in these subgroups. The CHMP suggested that these differences might be driven by the use of the non-validated once-daily lopinavir/ritonavir regimen. The influence of suboptimal exposure could be the underlying reason for the observed differences in response and failure (and not, in fact, the better response to darunavir/ritonavir treatment). However, this did not influence the primary outcome of non-inferiority.

Another potential limitation of the pivotal study is that all patients received a background regimen that was fixed rather than optimised.

The study population was broader than that advocated by the British HIV Association (BHIVA), which recommends treatment with boosted PIs only for patients in whom a non-nucleoside reverse transcriptase inhibitor is unsuitable. There are no efficacy and safety data for darunavir in these specific patient groups.

Darunavir/ritonavir (two tablets and one capsule) can be administered once daily. Unlike some PIs, in particular atazanavir, it does not interact with proton-pump inhibitors and H_2 antagonists.

Summary of comparative health economic evidence

The manufacturer supplied a lifetime cost-utility Markov model with cycles of 3 months duration. This adapted a model developed for the previous darunavir and etravirine SMC submissions in treatment-experienced patients permitting additional first and second-lines of treatment for ART naïve patients. This estimated the cost-effectiveness of darunavir/ritonavir compared to lopinavir/ritonavir as per the pivotal trial, and compared to atazanavir/ritonavir. These were appropriate comparators.

The extent of viral suppression was based upon 24-week data from the pivotal trial for the comparison of darunavir/ritonavir with lopinavir/ritonavir. A trial reported within the literature comparing atazanavir/ritonavir with lopinavir/ritonavir enabled an indirect comparison, and estimation of the rate of those achieving viral suppression at 24 weeks for atazanavir/ritonavir. CD4 cell count increases for the three viral load states within the modelling were estimated from the pivotal trial, this pooling data between the two arms.

The duration of maintenance of long-term virological response and treatment with lopinavir/ritonavir was estimated from response rates in the pivotal trial, coupled with data from a paper in the literature. Data from the pivotal trial resulted in darunavir/ritonavir being estimated to have a hazard ratio for cessation of treatment of 0.655 between weeks 24 and 96 compared with lopinavir/ritonavir. This resulted in those achieving virological suppression with darunavir/ritonavir at 24 weeks being estimated to maintain this for another 8 years, as compared with only 5 years for lopinavir/ritonavir. The maintenance of virological suppression and treatment with atazanavir/ritonavir was assumed to be the same as for darunavir/ritonavir.

Utility values were drawn from a standard reference within the literature, while non-ART treatment costs were drawn from an analysis of the UK HIV-AIDS National Prospective Monitoring Systems (NPMS) dataset.

The central estimates that resulted were that darunavir/ritonavir was £5,340 cheaper than lopinavir/ritonavir while also resulting in an average patient benefit of 0.28 QALYs. As a consequence, darunavir/ritonavir was estimated to dominate lopinavir/ritonavir. This result stemmed from an assumed longer duration of viral suppression and a delay in moving to more expensive third and fourth-line treatments.

Similarly, darunavir/ritonavir was estimated to be £906 cheaper than atazanavir/ritonavir, while resulting in an average patient benefit of 0.043 QALYs and so also dominating atazanavir/ritonavir.

Weaknesses of the analysis included:

- Assuming cessation of treatment among non-responders at 24 weeks despite continued increases in response rates to 48 weeks, though this may have been to the detriment of darunavir;
- Questionable extrapolation of the risk of loss of virological suppression between weeks 24 and 96 to yield the estimated additional 3 years maintenance of virological response for darunavir/ritonavir;

Despite these issues, the economic case was considered demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- HIV Scotland
- Waverly Care

Additional information: guidelines and protocols

The BHIVA guidelines for the treatment of HIV-1 infected adults with antiretroviral therapy were published in 2008, and predate the licensing of darunavir for treatment naïve adults. They advise that boosted PIs should ordinarily be reserved for specific groups of patients, such as those with primary NRTI and/or NNRTI resistance, women who wish to become pregnant, and in some patients with psychiatric problems.

Additional information: comparators

Current BHIVA guidelines recommend treatment with boosted PIs in combination with two NRTIs in ART naïve patients in whom efavirenz is not indicated. The BHIVA preferred boosted PI regimens are atazanavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir and saquinavir/ritonavir.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Darunavir plus ritonavir	**800mg darunavir plus 100mg ritonavir once daily**	**4,022**
Fosamprenavir plus ritonavir	700mg fosamprenavir plus 100mg ritonavir twice daily	4,153
Atazanavir plus ritonavir	300mg atazanavir plus 100mg ritonavir once daily	4,090
Saquinavir plus ritonavir	1,000mg saquinavir plus 100mg ritonavir twice daily	3,928
Lopinavir/ritonavir (Kaletra®)	Two tablets (200mg/50mg) twice daily	3,730

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 08.06.09.

Additional information: budget impact

The manufacturer estimated that 28 patients would receive treatment in year 1, rising to 351 in year 5 with a corresponding gross drug cost of £107k in year 1, rising to £1.34m by year 5. Drug cost offsets from reduced use of other protease inhibitors resulted in an estimated net drug cost of £6k in year 1, rising to £70k by year 5.

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 17 July 2009.

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.

**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/*

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Ortiz R, DeJesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1-infected patients at Week 48. AIDS 2008; 22:1389–97

Tibotec. Darunavir Clinical Research Report, TMC114-C211 (Week 96 interim analysis). November 2008

Mills A, Nelson M, Jayaweera D et al. Efficacy and safety of darunavir/ritonavir 800/100mg once-daily versus lopinavir/ritonavir in treatment-naïve, HIV-1-infected patients at 96 weeks: ARTEMIS (TMC114-C211) (Conference Report). Presented at the joint meeting of the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, and the 46th meeting of the Infectious Diseases Society of America, Washington, DC, USA, October 25–28 2008. http://www.natap.org/2008/ICAAC/ICAAC_17.htm

The European Medicines Agency (EMEA) Assessment Report Darunavir 400mg tablets (Prezista®). 20/11/2008, EMEA/H/C/707/X/16 www.emea.europa.eu