Scottish Medicines Consortium

darunavir 300mg tablets (Prezista®) No. (378/07)

Tibotec (a division of Janssen-Cilag Ltd)

4 May 2007

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

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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Darunavir, co-administered with 100mg ritonavir, is indicated, in combination with other antiretroviral medicinal products, for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor (PI).

Dosing information

600mg twice daily to be taken with ritonavir 100mg twice daily with food. Therapy should be initiated by a physician experienced in the management of HIV infection.

Product availability date

26 February 2007

Summary of evidence on comparative efficacy

Darunavir is a non-peptidic 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 efficacy of darunavir, boosted with ritonavir, was demonstrated in two pivotal, ongoing, phase IIb studies, supported by an open-label study. The two pivotal trials were randomised, partially-blinded, active-controlled, dose-finding studies of similar design, which compared darunavir/ritonavir with other currently available PIs in HIV-1 patients with limited treatment options and evidence of PI resistance. Patients had to be three-class experienced, defined as ≥1 PI for at least three months with evidence of ≥1 primary PI mutation (D30N, M46I/L, G48V, I50V/L, V82A/F/T/S, I84V, L90M), prior treatment with two or more nucleoside reverse transcriptase inhibitors (NRTIs) for at least 3 months in total and one or more non-nucleoside reverse transcriptase inhibitors (NNRTIs) as part of a failing regimen. Patients receiving treatment with an NNRTI at screening or taking medication which might interact with darunavir were excluded. Patients co-infected with hepatitis B and C could be recruited to the second of these studies only. The studies had three phases; screening, a dose-finding treatment period and an optimal dose treatment period. At screening the investigator selected an individualised treatment regimen consisting of ≥1 PI plus an optimised background regimen (OBR) of ≥2 NRTIs with or without enfuvirtide. Patients were stratified for baseline viral load, enfuvirtide use and number of primary PI mutations. Patients randomised to darunavir/ritonavir replaced the PI in their selected regimen with darunavir/ritonavir. Due to prior treatment experience, not all patients in the control group had a PI to which their virus was susceptible. These patients were recommended to use a new treatment regimen that included either a boosted PI or dual (boosted) PI combination. At least one PI had to be added to the OBR for control group patients. If these patients proved early failures they were allowed to roll over to the open-label study.

During the 24-week dose-finding period, patients were randomised to darunavir/ritonavir 400/100mg daily or 800/100mg daily or 400/100mg twice daily or 600/100mg twice daily or PI control. Interim analyses at 16- and 24-weeks established the optimal dose as 600mg/100mg twice daily and at 24 weeks, all darunavir patients were converted to the darunavir/ritonavir recommended dose, for a further 120 week, open-label phase. The primary outcome measure was confirmed virologic response, defined as a drop in plasma viral load of ≥1 $\log_{10}$ HIV-RNA versus baseline, at 24 weeks. Secondary outcome measures included the proportion of patients with ≥1 $\log_{10}$ decrease in viral load (compared to baseline) at other time points, the proportion of patients with plasma viral load <50 copies/ml over time and absolute change in CD4+ cell count over time and quality of life.

The intention to treat population included 278 and 317 patients from the two studies. Patients recruited to the first study had more advanced disease as evidenced by longer disease duration, treatment experience and lower mean CD4+ cell counts. In the studies, 49% and 28% of patients had ≥3 primary PI mutations at baseline and 71% and 63% were infected with virus with resistance to all available PIs. Enfuvirtide was used for the first time in 38% and 35% of patients as part of their OBR. The primary outcome results presented are for the combined analyses of the two studies and only for patients started on the recommended dose, darunavir/ritonavir 600mg/100mg twice daily (n=131) and the PI control regimen (n=124) at 24 weeks. Significantly more patients achieved the primary outcome in the darunavir/ritonavir group than the PI control group (70% vs 21%, p<0.001). Similarly, at 48 weeks, 61% of darunavir/ritonavir patients were still responders compared with 15% of PI control patients (p<0.001). Sensitivity analyses showed these 24- and 48-week results to be robust. The proportion of patients achieving a plasma viral load of <50 HIV-1 RNA copies/ml in the combined analysis was significantly higher in the darunavir/ritonavir group at both 24 and 48 weeks (45% vs 12% and 45% vs 10%, respectively, p<0.001) and there were significantly greater increases in CD4+ cell count at both time points (92 vs 17 cells/mm^3 and 102 vs 19 cells/mm^3 respectively, p<0.001). In the darunavir/ritonavir group, 21% of patients discontinued compared to 81% in the PI control group with 67% of these discontinuations due to virologic failure. Outcomes in the open-label study, at 24 and 48 weeks, were similar to those for the combined pivotal studies.

Summary of evidence on comparative safety

In the three clinical studies, the most common treatment-emergent adverse events associated with darunavir/ritonavir compared with the PI control were diarrhoea (16% vs 28%), nausea (12% vs 13%), nasopharyngitis (12% vs 11%) and headache (11% vs 20%).

The majority of adverse events were grade 1 or 2 in severity, although 29% of patients reported grade 3 or 4 adverse events in both the darunavir/ritonavir and PI control groups. A few cases of pancreatitis grade 3 or 4 have been observed which may possibly be related to darunavir.

There are no data on the safety of darunavir/ritonavir co-administration with NNRTIs as they were excluded from the trials as well as medications that might be expected to have clinically significant interactions with darunavir. No safety concerns emerged in patients co-infected with hepatitis B and C but numbers included were small. There was a higher incidence of grade 3-4 triglyceride and grade 3 cholesterol laboratory abnormalities in the darunavir/ritonavir group compared to controls.

Summary of clinical effectiveness issues

The development of drug-resistant mutations and the increase in transmitted resistance in patients with HIV infection compromises the durability of response to treatment. Darunavir in combination with an OBR has been shown to provide a significantly improved virologic response in significantly more patients at 24 weeks than a comparator PI control plus OBR in treatment experienced patients. However, despite combining analyses from both pivotal studies the number of patients for whom results are available for the recommended dose of darunavir is still relatively small, 131 patients, 21 of whom had discontinued by week 48. As expected discontinuations in the PI control group were high with 92 of the 124 patients having discontinued at 48 weeks.

Darunavir is a strong inhibitor of CYP3A4 and patients taking concomitant medicines that might have interacted with darunavir were excluded from the studies. Therefore information on the concomitant use of these drugs with the recommended dose of darunavir and the use of darunavir in combination with other PIs is still awaited. Patients co-infected with hepatitis B and C were recruited to the second pivotal study, and although the results did not suggest any adverse impact of co-infection on virological response rate the number of patients was small. The EMEA concluded that further characterisation of the safety profile of darunavir was required and this would be addressed in the risk management plan and final results of the ongoing studies as part of the measures to be fulfilled post-authorisation.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing darunavir to the mix of medicines used in patients in the control arm of the pivotal clinical trials. A Markov model was used to combine data on CD4+ cell count and virological response and hence to make lifetime estimates of the costs and benefits of using darunavir. The net lifetime NHS cost was estimated at £22,142 and the lifetime QALY gain at 1.4. The net cost per QALY gained was thus £15,682. In a sensitivity analysis darunavir was also compared to tipranavir and the net cost per QALY gained was estimated to be £12,473.

In terms of the design of the economic evaluation an appropriate comparator treatment pathway was selected. Markov modelling based on CD4+ cell count was appropriate. The manufacturer was able to show that the model's predictions were in line with the observed randomised control trial results after one year of treatment. It was also demonstrated that while several clinical studies had been used to populate the model there was an acceptable degree of consistency between these in terms of patient and disease characteristics.

There was some concern about the utility values used, in that advanced stages of the disease still have quite high values. However, it seemed likely that lowering these values to a level that would reflect clinical experience would count in favour of the more effective treatment, which in this case appeared to be darunavir.

Summary of patient and public involvement

Patient Interest Group Submission: HIV Scotland

Additional information: guidelines and protocols

British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2005). An update to these guidelines was published in 2006.

Additional information: previous SMC advice

In September 2006, following a resubmission, the SMC recommended that tipranavir (Aptivus) in combination with low dose ritonavir is accepted for restricted use within NHS Scotland for the treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors. At 48 weeks, tipranavir, in combination with low dose ritonavir, showed a significant improvement in the reduction of viral load compared with other protease inhibitor plus ritonavir regimens. Although the overall rate and type of adverse events were similar, tipranavir had a higher incidence of hepatotoxicity, hyperlipidaemia, bleeding events and rash. Tipranavir is more expensive than other protease inhibitors and it is restricted to patients with a tipranavir mutation score of less than 4.

Additional information: comparators

Other boosted PIs

Additional information: costs

Medicine	Dose	Daily treatment cost	Annual treatment cost
Darunavir + ritonavir	**600mg + 100mg twice daily**	**£17**	**£6235**
Tipranavir + ritonavir	500mg + 200mg twice daily	£21	£7580
Atazanavir + ritonavir	300mg +100mg twice daily	£23	£8476
Fosamprenavir + ritonavir	700mg +100mg twice daily	£11	£4151
Saquinavir + ritonavir	1g + 100mg twice daily	£11	£4051
Lopinavir / ritonavir	400mg /100mg twice daily	£10	£3729
Amprenavir + ritonavir	600mg + 100mg twice daily	£9	£3354

Costs are from the eVadis database accessed on March 6, 2007. Doses are for general comparison and do not imply therapeutic equivalence.

Additional information: budget impact

According to the manufacturer's submission, the gross drug cost was estimated as £181k in year one rising to £394k by year 5. The net drug cost was estimated as £42k in year one rising to £92k by year 5.

778 HIV patients were estimated to have experienced at least two protease inhibitors in year one, of whom 30% or 233 were estimated to switch from their current protease inhibitor. Given the rising incidence of HIV the numbers having experience of two protease inhibitors and requiring a switch from their current therapy was anticipated to rise to 338 by year 5. The market share assumed was 12% in year one, or 29 patients, rising to 19%, or 63 patients, by year five. Information received from SMC clinical experts suggests that these figures may be an overestimate of patient numbers.

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 12 April 2007.

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.

Scientific Disscussion. Prezista® http://www.europa.eu