Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

darunavir 400mg tablets (Prezista®) SMC No. (707/11)
Janssen

08 July 2011

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

darunavir (Prezista®) 400mg is accepted for use within NHS Scotland.

Indication under review: darunavir 800mg once daily co-administered with low dose ritonavir (100mg once daily) for the treatment of HIV-1 infection in antiretroviral therapy experienced adults with no darunavir resistance associated mutations and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells/mm^3.

Darunavir 800mg/ritonavir 100mg once daily was demonstrated to be non inferior to darunavir 600mg/ritonavir 100mg twice daily, when administered with an optimised background regimen that consisted of at least two nucleoside reverse transcriptase inhibitors in treatment experienced HIV infected patients.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Darunavir 800mg once daily co-administered with low dose ritonavir (100mg once daily) for the treatment of HIV-1 infection in antiretroviral therapy experienced adults with no darunavir resistance associated mutations and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells/mm^3.

Dosing Information

Darunavir 800mg once daily with ritonavir 100mg once daily taken with food.

Therapy should be initiated by a physician experienced in the management of HIV infection. Patients should be instructed to take darunavir with low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir.

Product availability date

7 March 2011

Summary of evidence on comparative efficacy

Darunavir is a non-peptidic protease inhibitor (PI) with activity against wild type Human Immunodeficiency Virus-1 (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.

A multi-centre, randomised open-label phase III study has been conducted in treatment-experienced, HIV-1 infected adult patients with a plasma HIV-1 RNA > 1,000 copies/mL, a CD4 count > 50 cells/mm^3 and no baseline darunavir resistance associated mutations. Patients were also required to be receiving a stable highly active anti-retroviral therapy (HAART) regimen for at least 12 weeks. Patients were randomised equally (stratified by HIV-1 RNA [≤ or > 50,000 copies/mL]) to darunavir 800mg/ritonavir 100mg once daily or darunavir 600mg/ritonavir 100mg twice daily. All patients received an optimised background regimen (chosen by the investigator prior to randomisation) that consisted of at least two nucleoside reverse transcriptase inhibitors (NRTIs) based on anti-retroviral history and resistance testing. The study included a screening period that lasted up to four weeks, a 48 week treatment period and a four-week follow-up period.

The primary outcome was virological response defined as a confirmed plasma viral load of < 50 copies/mL at week 48, using the time to loss of virological response (TLOVR) algorithm and a non-inferiority margin of -12%. The TLOVR algorithm consisted of the following: response and loss of response had to be confirmed at two consecutive visits and patients who prematurely discontinued were considered as non responders after withdrawal. Patients with intermittent missing viral load values were considered responders if the preceding and succeeding visits indicated response. In all other cases, intermittent values were imputed with non-response. Re-suppression after confirmed virologic failure was considered as failure in this algorithm. The intent-to-treat (ITT) population that included all randomised patients who took at least one dose of study medication irrespective of protocol compliance was used for the non-inferiority analysis.

A total of 590 patients were randomised and the proportions of patients who completed week 48 were 86% (253/294) and 84% (248/296) for the once and twice daily darunavir dose regimens respectively. At week 48 a virological response was observed in 72.1% of patients in the once daily group versus 70.9% in the twice daily group (estimated difference in response 1.2%, 95% confidence interval [CI] -6.1 to 8.5), demonstrating the non-inferiority of darunavir 800mg/ritonavir 100mg once daily with darunavir 600mg/ritonavir 100mg twice daily.

Secondary endpoints included change in CD4 cell count from baseline to week 48, virological failures, patient adherence and quality of life (QoL). The least square mean change in CD4 count from baseline to week 48 was 107 cells/mm^3 versus 113 cells/mm^3 for the once daily and twice daily groups respectively. There were 65 (22%) versus 54 (18%) virological failures in the once daily and twice daily groups respectively. In the once daily group there were 54 non responders and 11 re-bounders and in the twice daily group there were 43 non-responders and 11 re-bounders. One patient developed PI mutations which included darunavir resistance associated mutations.

Patient adherence was similar for both groups; mean four to 48 week adherence, measured using the modified-medication adherence self report inventory questionnaire, was 63% for the once daily group and 56% for the twice daily group. In the functional assessment of HIV infection questionnaire used to assess QoL, there were no statistically or clinically relevant differences between the two groups for mean changes at week 48 compared to baseline.

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

Summary of evidence on comparative safety

No new adverse events were reported. The safety results of the study were consistent with the known safety profile of darunavir 600mg/ritonavir 100mg twice daily regimen.

The proportion of patients who reported at least one adverse event (AE) was 76% (224/294) in the once daily group and 77% (228/296) in the twice daily group. AEs that were considered at least possibly related to darunavir and with a incidence of ≥ 2% included; nausea (10.9% [32/294] versus 10.5% [31/296]), diarrhoea (9.9% [29/294] versus 15% [45/296]), vomiting (3.1% [9/294] versus 5.4% [16/296]), rash (2.7% [8 patients] each) and headache (1.4% [4/294] versus 2.0% [6/296]) for the once daily versus twice groups respectively. Laboratory abnormalities were low and similar between groups with the greatest difference being for triglyceride elevations (5.2% [15/294] versus 11% [31/296], $p<0.05$). Total and LDL-cholesterol levels were also significantly lower in the once daily than the twice daily group. Serious AEs occurred in 5.4% (16/294) of patients in the once daily group compared to 9.1% (27/296) of patients in the twice daily group. There were eight deaths during the study and none were considered related to study treatment.

Summary of clinical effectiveness issues

The indication under review is once daily administration of darunavir 800mg (with ritonavir 100mg) in treatment experienced patients with no darunavir resistance associated mutations and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells/mm^3.

SMC have previously accepted darunavir 600mg twice daily (with ritonavir 100mg twice daily) for use in the treatment of HIV-1 infection in highly pre-treated adult patients who have failed on more than one regimen containing a protease inhibitor (PI). This indication has been amended by the regulatory authorities. Darunavir 600mg twice daily (with ritonavir 100mg twice daily) is now indicated for the treatment of HIV-1 infection in antiretroviral treatment (ART) experienced adult patients, including those that have been highly pre-treated (and including patients in whom HIV-1 genotype testing is not available). The company has indicated that they do not intend to make a submission to SMC for this indication. However there is considerable overlap between the current indications for ART experienced adults and the indication (for highly pre-treated adult patients who have failed on more than one regimen containing a PI) previously accepted for use by SMC. This effectively means that there will be only a small sub-group of patients eligible for darunavir but for whom there will be no SMC advice available.

Non-inferiority of the once daily regimen over the twice daily regimen was demonstrated for virological response in the pivotal study. However the study has some limitations. Firstly, it used a non-inferiority margin of 12%. Although EMA made no comment regarding this margin, British HIV Association guidelines commented generally that a non-inferiority margin of 10% to 15% for studies was high. Secondly, the study duration was 48 weeks, which the EMA considered to be inadequate, and therefore the long-term efficacy of the once daily darunavir regimen in anti-retroviral therapy (ART) experienced adult patients with no darunavir resistance associated mutations is unknown. It should be noted that the studies of PI included in the mixed treatment comparison had a similar duration.

A sub-group of the study population supports the indication under review. The EMA was concerned regarding the outcome in certain sub-groups of the pivotal study and consequently restricted the indication to ART experienced adults with HIV-1 RNA <100,000 copies/ml and CD4+ cell count ≥100 cells/mm^3. Although the study does not have sufficient power to demonstrate non-inferiority in this sub-group the EMA were satisfied with the clinical data to grant marketing authorisation.

The administration schedule for the indication under review is once daily which may have benefits in terms of treatment adherence. However, adherence was assessed in the study using three measures and there was no significant difference between the once daily and twice daily groups. One of the key comparators, atazanavir, may also be administered once daily. Adherence to ART is important in terms of obtaining optimal benefit from treatment. In the study virologic response at week 48 was approximately 10% greater for adherent patients compared to the full ITT population. The EMA raised concerns regarding the extent of non-compliance/non-adherence but did acknowledge that the robustness of the non-inferiority conclusion was not compromised.

The comparative efficacy of the darunavir once daily regimen is unknown except versus the darunavir twice daily regimen. In their submission to SMC the company included a mixed treatment comparison (MTC) to indirectly compare darunavir/ritonavir, lopinavir/ritonavir and atazanavir/ritonavir. Limitations of the MTC include the following; heterogeneity between studies in terms of prior treatments and some outcome measures and in addition some of the included studies were conducted up to 10 years ago. Comparative evidence is not clear from the MTC but efficacy results look similar with all confidence intervals overlapping.

Summary of comparative health economic evidence

The submitting company presented two cost-utility analyses comparing darunavir/ritonavir 800mg/100mg once daily with atazanavir/ritonavir 300mg/100mg once daily and with lopinavir/ritonavir 400mg/100mg twice daily. All regimes were in addition to optimised background regimen (OBR). Consideration was also given to the subsequent treatment of patients with two further treatments being possible.

A Markov model was used to estimate costs and benefits over the lifetime of a cohort of patients with the same characteristics at baseline as in the main clinical study. Effectiveness data for darunavir were taken from the sub-group of the clinical study that reflected the new licence. A mixed treatment comparison was carried out of the three treatment options in terms of effectiveness and tolerance. Effectiveness data included the change in CD4 cell counts and virologic response. The structure of the model had been used in previous submissions to SMC.

Costs included the costs of all the medicines used, including subsequent medicines treatment, and an estimate of the NHS costs of managing the disease. Data for the latter category came from an analysis of NHS data for 2000-2006. Utility data were taken from a published paper giving an overview of 21,000 patients in HIV clinical trials who had completed an EQ-5D questionnaire; values were applied for each banding of CD4 cell counts. Costs were updated to current values where necessary and results were discounted at 3.5% per annum.

Compared to atazanavir, the lifetime NHS costs were £871 lower with darunavir (£243,374 versus £244,244) while the quality adjusted life year (QALY) gain was 0.155 (13.743 QALYs versus 13.5880). This means that darunavir was estimated to dominate atazanavir (i.e. cheaper and more effective); however, the company noted that differences should be interpreted with caution as they were small differences between large totals. The company suggested that a plausible interpretation is that darunavir and atazanavir are similar in economics terms. Compared to lopinavir, the lifetime NHS costs were £1,002 higher with darunavir (£243,374 versus £242,371) while the QALY gain was 0.044 (13.743 QALYs versus 13.699) resulting in a cost per QALY of £22,871. Again, the company suggested the differences were small.

Sensitivity analyses suggested that the base case results were relatively robust. However, the main issue was that the mixed treatment comparison showed there was no significant difference in efficacy or tolerance across the three treatments; the differences in QALYs were generated by point estimates that were not statistically significantly different from each other. The darunavir option was cheaper than the atazanavir option so even if equivalence had been assumed this would not matter. However, the darunavir option was more expensive than lopinavir so equivalence in terms of efficacy and tolerance would mean it was not preferred on economics grounds. However, clinical experts consulted by SMC suggest the darunavir option may be more tolerable, even though this was not demonstrated on the mixed treatment comparison: given the very small difference in costs, this difference may well be sufficient to support the case for cost-effectiveness.

While this was recognized to be a limitation, the economics case was accepted as being demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from HIV Scotland.

Additional information: guidelines and protocols

British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy were published in 2008. The guidelines recommend that "HAART regimens always need to be individualized for the patient in order to achieve the maximum potency, durability, adherence and tolerability and to avoid long term toxicities and any likely drug interactions. It is therefore essential to undertake a full baseline assessment before starting treatment and this should include HIV resistance testing, and screening for hepatitis B and C co-infection. In addition, a full cardiovascular risk assessment should be undertaken and patients should be screened for diabetes and renal problems as well as having a psychosocial history taken to identify psychiatric problems, alcohol use and recreational drug use. The goal of treatment must always be to achieve a viral load of < 50 copies/mL and to achieve this within 4 to 6 months of starting treatment. Boosted PIs should be reserved for specific groups of patients, such as those with primary nucleoside reverse transcriptase inhibitor (NRTI) and/or NNRTI resistance, women who wish to become pregnant, and some patients with psychiatric problems."

Boosted PIs included in the guidelines are lopinavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir, atazanavir/ritonavir and darunavir/ritonavir. Boosted PIs may be used in all patient populations including those who are treatment experienced.

Additional information: comparators

Other boosted PIs (with ritonavir) that are used in treatment experienced patients include lopinavir, atazanavir, fosamprenavir, and saquinavir.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
darunavir/ritonavir	**darunavir 800mg plus ritonavir 100mg once daily**	**3,849**
atazanavir/ritonavir	atazanvir 300mg plus ritonavir 100mg once daily	3,917
fosamprenavir/ritonavir	fosamprenavir 700mg plus ritonavir 100mg twice daily	3,614
saquinavir/ritonavir	saquinavir 1,000mg plus ritonavir 100mg twice daily	3,520
lopinavir/ritonavir	lopinavir 400mg plus ritonavir 100mg twice daily	3,463

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27 April 2011. Annual cost of darunavir 600mg plus ritonavir 100mg twice daily is £5,892.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 1,650 patients in year 1 rising to 2,284 in year 5. Based on an estimated uptake of 20% in year 1 and 40% in year 5, the gross impact on the medicines budget was estimated at £1.1m in year 1 and £3.2m in year 5. The main saving was in terms of other medicines displaced (e.g. atazanavir). The net medicines budget impact was estimated at £16K and £45K.

References

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

Cahn P, Fourie J, Grinsztejn B, Hodder S, Molina JM, Ruxrungtham K, et al. ODIN: 48-week analysis of once- versus twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients. AIDS 2011 Feb 22

European Medicines Agency. CHMP Assessment Report; darunavir. Type II variation. Procedure No. EMEA/H/C/ 000707/II/0032. 20 January 2011.

This assessment is based on data submitted by the applicant company up to and including 27 May 2011.

**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/About_SMC/Policy_Statements/Policy_Statements*

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.

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.