All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Darunavir (Prezista®▼) for the treatment of HIV-1 infected, treatment-naïve adults in combination with other antiretroviral medicinal products

Janssen-Cilag Limited

Advice No: 2009 – December 2009

Recommendation of AWMSG

Darunavir (Prezista®▼) co-administered with low dose ritonavir is recommended as an option for use within NHS Wales for the treatment of human immunodeficiency virus (HIV)-1 infection in treatment naive patients.

AWMSG is of the opinion that darunavir (Prezista®▼) is not suitable for shared care within NHS Wales.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 16th December 2009

The recommendation of AWMSG is:

Darunavir (Prezista®▼) co-administered with low dose ritonavir is recommended as an option for use within NHS Wales for the treatment of human immunodeficiency virus (HIV)-1 infection in treatment naive patients.

AWMSG is of the opinion that darunavir (Prezista®▼) is not suitable for shared care within NHS Wales.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Darunavir (Prezista®▼) 400mg, 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[1].

2.2 Dosing

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

Darunavir is administered orally as 400mg film-coated tablets. The recommended dose in treatment-naïve adult patients is 800mg once daily, taken with ritonavir 100 mg once daily and with food. Darunavir is not recommended for use in treatment-naïve children and adolescents, and should be used with caution in the elderly due to the limited data that are available. No dose adjustment is required in renal impairment, or in mild-to-moderate hepatic impairment, although it should be used with caution in this latter group. Darunavir should not be used in patients with severe hepatic impairment. See the Summary of Product Characteristics (SPC) for full details[1].

2.3 Market authorisation date

Darunavir (at a dose of 600mg twice daily) was first licensed in Europe for use in treatment-experienced patients in February 2007[2]. A license for the 400mg tablets, for use in treatment-naïve patients at a dose of 800mg once daily, was granted in January 2009[3].

2.4 UK Launch date

Darunavir was first launched in 2007. The 400mg formulation for use in treatment-naïve patients was launched in February 2009[1].

3.0 DECISION CONTEXT

The 2008 British HIV Association (BHIVA) guidelines emphasise that highly active antiretroviral treatment (HAART) regimens must be individualised for patients with HIV-1 in order to achieve the maximum potency, durability, adherence and tolerability, and to avoid long term toxicities and any likely drug interactions[4]. A HAART regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs), in addition to a non-nucleoside reverse transcriptase inhibitor (NNRTI) (preferably efavirenz), is the generally preferred first-line regimen in newly diagnosed HIV-1 patients in whom treatment is recommended. In patients who experience first virological failure on this type of regimen, it is generally recommended that the regimen is switched to one including two different NRTIs plus a boosted protease inhibitor (PI). The BHIVA guidelines recommend that first-line use of boosted PIs should usually 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[4]. However, the choice of any regimen should be guided by the results of resistance testing, and other factors such as the ability of the patient to adhere to and tolerate individual drugs[4].

There are several PIs available and they differ in terms of their convenience, drug interactions, tolerability and adverse effect profiles, and their licensed indications[4]. Those that are licensed for use in both treatment-experienced and treatment-naïve patients include fosamprenavir (Telzir®)[5], saquinavir (Invirase®)[6], lopinavir (co-formulated with ritonavir as Kaletra®)[7], and atazanavir (Reyataz®)[8]. Darunavir

(Prezista®)[1] was originally licensed only for treatment-experienced patients, and the license was extended in January 2009 to include treatment-naïve patients[3]. The Welsh Medicines Partnership (WMP) identified lopinavir and atazanavir as the most appropriate comparators for darunavir in treatment-naïve patients[9].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The phase III, randomised, non-inferiority ARTEMIS trial supports the use of darunavir in treatment-naïve patients. This compared once daily darunavir 800mg/ritonavir 100mg against lopinavir 800mg/ritonavir 200mg per day. Over 48 weeks, darunavir/ritonavir was shown to be non-inferior to lopinavir/ritonavir for the primary endpoint of proportion of patients with undetectable HIV ribonucleic acid (RNA) (defined as <50 copies/mL), and the secondary virological and immunological endpoints. Sub-group analyses suggested a favourable response to darunavir/ritonavir in patients with high baseline viral load and low CD4 cell counts; however, these analyses should be interpreted with caution as around 25% of lopinavir/ritonavir recipients received a once daily regimen that is not currently licensed in Europe, is rarely used in practice in Wales and may have been sub-optimal. Exploratory analyses conducted only in those patients who received the Europe-licensed twice daily lopinavir/ritonavir regimen confirmed the non-inferiority for the primary endpoint. At 96 weeks of follow-up, the proportion of patients with HIV RNA <50 copies/mL was statistically superior with the darunavir regimen.

No new safety signals were identified in the treatment-naïve population of the ARTEMIS trial. The incidence of gastro-intestinal adverse effects, and increases in total cholesterol, triglycerides and HDL-cholesterol, were significantly lower with darunavir/ritonavir compared with lopinavir/ritonavir.

4.2 Review of the evidence on cost-effectiveness

A Markov-model based cost utility analysis is described, in which darunavir/ritonavir is compared against lopinavir/ritonavir as first-line treatments as per the ARTEMIS trial. Following first-line treatment failure, patients follow a treatment path of three other regimens before death.

The model estimates that darunavir/ritonavir is both more effective and less costly than lopinavir/ritonavir (i.e. darunavir dominates lopinavir treatment) in the base-case analysis and in all one-way sensitivity analyses that were conducted in the original company submission. The key parameter driving model outputs is the duration of the CD4 stable/slow increase stage, which in the base-case analysis is modelled to be three years longer for darunavir/ritonavir compared with lopinavir/ritonavir based on a non-statistically significant difference in the time to virological failure observed in exploratory analyses of the ARTEMIS trial data. Further analyses provided by the company indicate that when the assumed additional duration of the CD4 stable/slow increase stage for darunavir/ritonavir is reduced to three months, the model outputs switch from darunavir/ritonavir being the dominant strategy to having an incremental cost per QALY gained of £26,780 compared with lopinavir/ritonavir. The combined impact of the uncertainty in this key parameter and other parameters has not been explored.

A scenario analysis has been conducted in which atazanavir/ritonavir is modelled as the first-line comparator. In this analysis, the duration of the CD4 stable/slow increase stage is assumed to be the same for both treatments. Sensitivity analyses indicate that this model is very sensitive to several key parameters to the extent that darunavir

switches from being dominant over atazanavir in the base case analysis, to having an incremental cost per quality adjusted life year (QALY) gained in excess of £30,000.

5.0 LIMITATIONS OF DECISION CONTEXT

- Baseline primary drug resistance was low in the treatment-naïve population of the ARTEMIS trial. The BHIVA guidelines suggest that first-line use of boosted PIs should usually be reserved for specific groups of patients, such as those with primary NRTI and/or NNRTI resistance.

6.0 CLINICAL EVIDENCE

6.1 Efficacy

The pivotal efficacy data are derived from the ongoing open-label, phase III, non-inferiority ARTEMIS trial[10]. Of 843 patients who were screened for inclusion, 691 ART-naïve patients were randomised (1:1) to receive once daily darunavir 800mg/ritonavir 100mg or lopinavir 800mg/ritonavir 200mg per day[2] (given as a once daily regimen not licensed in Europe, or as lopinavir 400mg/ritonavir 100mg twice daily as licensed in Europe, depending on local licensing[10]). All patients also received a fixed background NRTI regimen of tenofovir DF 300mg/emtricitabine 200mg[10]. Eligible patients had plasma HIV-1 RNA of at least 5,000 copies/mL and randomisation was stratified by baseline plasma viral load and CD4 cell counts. The baseline characteristics, and key efficacy data, are summarised in Table 1A in Appendix 1.

At 48 weeks, the proportion of patients achieving and maintaining a HIV RNA load <50 copies/mL (the primary endpoint) was 83.7% for darunavir/ritonavir treatment versus 78.3%[2]. The difference in treatment responses was 5.6% (95% confidence interval [CI]: -0.1 to 11); since the lower limit of the 95% CI was greater than -12% the criterion for demonstration of non-inferiority of darunavir/ritonavir against lopinavir/ritonavir was met, but superiority was not demonstrated across the entire arms (p=0.062)[10]. When assessed by baseline stratification factors, patients with a higher baseline viral load (≥100,000 copies/mL), constituting approximately a third of the trial population, seemed to respond better to treatment with darunavir/ritonavir compared with lopinavir/ritonavir. There were no statistically significant differences observed for the secondary endpoints of the proportion of patients with HIV RNA <400 copies/mL, and the mean change from baseline in HIV RNA load and CD4 cell counts, which had improved in both groups at 48 weeks[2] (see Table 1A, Appendix 1). Virological failure at any point up to 48 weeks occurred in 9.9% of the darunavir/ritonavir group and 14.2% of the lopinavir/ritonavir group[2].

The company submission provides details of interim analyses conducted at 96 weeks[3]. These indicate that, across the entire treatment arms, the proportion of patients with HIV RNA maintained at <50 copies/mL was statistically superior with darunavir/ritonavir compared with lopinavir/ritonavir at 96 weeks[11], in contrast with the 48-week data. When 96 week data was assessed by baseline stratification factors, patients with a higher baseline viral load (≥100,000 copies/mL) and/or a lower baseline CD4 cell count (<200 copies/mm^3) seemed to respond better to treatment with darunavir/ritonavir compared with lopinavir/ritonavir[11]. The incidence of virological failure was less with darunavir/ritonavir compared with lopinavir/ritonavir (11.7% versus 17.1%[12]). The median change from baseline in CD4 counts continued to improve for both treatment arms, numerically more so for lopinavir/ritonavir[11] (see Table 1A, Appendix 1). More detail was provided but this remains commercial in confidence.

Health-related quality of life (HRQoL) was assessed in the ARTEMIS trial and remains commercial in confidence.

Points to note

- The company submission states that the ARTEMIS trial was conducted in an open-label fashion due to difficulties in obtaining a matching placebo for lopinavir/ritonavir and the significant increase in pill burden that patients would experience in an attempt to achieve double-blinding[3]. The Committee for Medicinal Products for Human Use (CHMP) considered that the open-label design did not affect the major outcomes of the study, including conclusions on efficacy and safety[2].
- There was some variation in response to treatments according to region. In Europe there was less response in the darunavir/ritonavir group compared with the lopinavir/ritonavir group (difference in proportions achieving HIV RNA <50 copies/mL: -4.3; 95% CI: -15.5 to 6.9[2], which is outside of the definition of non-inferiority), whilst in other regions the response in the darunavir/ritonavir group appears to be improved compared with the lopinavir/ritonavir group. The CHMP considered that a likely explanation for this difference is that, in Europe, the discontinuation rate for darunavir/ritonavir was higher than for lopinavir/ritonavir (13% versus 10.0%), whereas for the other regions the discontinuation rate for darunavir/ritonavir was lower than for lopinavir/ritonavir. However, the numbers in these groups were small and the differences between treatment arms not significant[2].
- The CHMP considered that the differential response to darunavir/ritonavir in terms of baseline stratification factors and region, and the numerically favourable rates of virological failure observed with darunavir/ritonavir compared with lopinavir/ritonavir, should be interpreted with caution due to the use of the once daily lopinavir/ritonavir regimen in a substantial proportion of patients. (see section 7.2)
- Baseline drug resistance was low in this treatment-naïve population. At screening and/or baseline 1.6% harboured at least one PI resistant mutation and 3.6% harboured at least one NRTI resistant mutation[12]. No patients failing therapy on either treatment developed primary PI mutations up to 96 weeks, and isolates remained fully susceptible to all PIs[12].

6.2 Safety and tolerability

Darunavir was appraised by AWMSG for treatment-experienced HIV-1 infected patients in 2007[13]. No new safety signals were identified in the treatment-naïve population of the ARTEMIS trial and the safety and tolerability appears similar to that seen with other boosted PIs[2].

Over 90% of patients experienced at least one adverse event in the ARTEMIS trial up to 48 weeks[10]. The most common was diarrhoea, which was reported in 23.0% of patients on darunavir/ritonavir and in 46.5% of patients on lopinavir/ritonavir treatment[2]. Other commonly reported adverse events that occurred more frequently with lopinavir/ritonavir than with darunavir/ritonavir treatment included nausea (25.1% versus 13.7%, respectively), headache (7.8% versus 6.1%), abdominal pain (6.6% versus 3.5%) and vomiting (7.8% versus 3.2% respectively)[2]. The exception was the overall incidence of rash-related adverse events, which was 5.5% in the darunavir/ritonavir group versus 2.9% in the lopinavir/ritonavir group[2].

The company submission reports 96-week data from ARTEMIS. The incidence of grade 2-4 adverse events (excluding laboratory parameters) thought to be possibly related to treatment was 23% with darunavir/ritonavir treatment compared with 34%

with lopinavir/ritonavir[11]. The most common were gastro-intestinal adverse events which occurred most frequently with lopinavir/ritonavir than with darunavir/lopinavir (15% versus 7%)[11]. These included diarrhoea (11% versus 4%; p<0.001) and nausea (3% versus 2%). Rash considered possibly treatment-related occurred in 3% of the darunavir/ritonavir group compared with 1% of the lopinavir/ritonavir group[11]. No cases of rash occurred between weeks 48 and 96 in the darunavir group[11].

Both treatment regimens resulted in increased lipid parameter values, although darunavir/ritonavir was associated with a less negative lipid profile over the course of the study than lopinavir/ritonavir. The respective mean percentage increases from baseline in total cholesterol (15% versus 23%; p<0.001), triglycerides (12% versus 50%; p<0.001) and high density lipoprotein (HDL)-cholesterol (15% versus 19%; p=0.0102) were statistically significantly lower with darunavir/ritonavir than with lopinavir/ritonavir, and were numerically but not statistically lower for low density lipoprotein (LDL)-cholesterol (14% versus 18%)[11]. The company submission notes that the differential increase in triglycerides may be partly related to the higher ritonavir dose used in the lopinavir arm of the study[3]. It is reported that a higher proportion of patients in the lopinavir/ritonavir group experienced elevations in total cholesterol and triglycerides[3]. However, similar numbers of patients in each arm used lipid-lowering agents (7-8%)[11]. There were no clinically relevant changes in body weight or shape reported for either treatment arm[3].

The company submission reports that serious adverse events possibly related to treatment occurred less frequently with darunavir/ritonavir treatment than with lopinavir/ritonavir treatment (0.9% versus 2.9%)[3]. Discontinuations due to adverse events were lower in the darunavir/ritonavir group (4% versus 9%)[11] and included six deaths (one in the darunavir/ritonavir group)[11], none were considered to be treatment related[3].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

There are several licensed PIs available, as discussed in section 3.0. Those that are licensed for use in treatment-naïve patients include lopinavir (co-formulated with ritonavir, Kaletra®)[7], fosamprenavir (Telzir®)[5], saquinavir (Invirase®)[6] and atazanavir (Reyataz®)[8], and now darunavir (Prezista®)[1].

WMP identified lopinavir and atazanavir as the most appropriate comparator PIs for darunavir in treatment-naïve patients[9].

7.2 Comparative effectiveness

- The ARTEMIS trial demonstrated that darunavir 800mg/ritonavir 100mg once daily was non-inferior to lopinavir 800mg/ritonavir 200mg per day in reducing viral load to undetectable levels (HIV RNA <50 copies/mL) in treatment-naïve patients at 48 weeks. This was supported by secondary virological and immunological endpoint data. At 96 weeks of follow-up, the proportion of patients with HIV RNA <50 copies/mL was statistically superior with the darunavir regimen.
- A proportion of patients in the ARTEMIS trial received a once daily regimen of lopinavir/ritonavir, which is not currently licensed in Europe. The 2008 BHIVA guidelines note that evidence supports once daily administration of lopinavir/ritonavir in treatment-naïve patients[4], although expert opinion sought suggests this occurs rarely in practice. The company conducted exploratory analyses in only those patients who received the twice daily lopinavir/ritonavir

regimen that is approved in Europe. This produced results similar to the overall patient population[3]. Although sub-group analyses suggest a differential response to darunavir/ritonavir in patients with high baseline viral load and low CD4 cell counts, the CHMP considered that these results should be interpreted with caution, as the once daily lopinavir/ritonavir regimen could have led to sub-optimal exposure and this could be the reason for the observed differences, rather than a better response to darunavir/ritonavir[2].

- Patients in this trial had low levels of drug resistance at baseline[12]. No patients failing therapy on either treatment developed primary PI mutations up to 96 weeks, and isolates remained fully susceptible to all PIs[12].
- PIs differ in terms of their tolerability, convenience, drug interactions and lipid profiles. The 2008 BHIVA guidelines include a summary comparative table of ritonavir boosted PIs (excluding tipranavir) based mainly on data from treatment-naïve patients (see Table 1)[4].

Table 1. Comparative table of ritonavir boosted PI profiles from 2008 BHIVA guidelines[4]

	Lopinavir	Saquinavir	Fosamprenavir	Atazanavir	Darunavir
Potency in naïve patients	++++	++++	++++	++++	++++
Durability data	++++	++	+++	++	++
Convenience	+++	++	+++	++++	+++
Tolerability	++	+++	++	+++	+++
Lipid profiles	+	++	+	+++	+++
Resistance barrier	++++	++++	++++	++++	++++
Interaction profile	+++	++	++	+	++
++++ Excellent; +++ very good; ++ moderately good; + not good; - poor					

- The CHMP reports that adherence to treatment, as measured by patient-completed questionnaire, was slightly higher with darunavir/ritonavir than with lopinavir/ritonavir in the ARTEMIS trial at 48 weeks (84% versus 79%)[2]. Besides darunavir[1], only atazanavir is specifically licensed for once daily administration[8].
- All PIs should be boosted with ritonavir[4]. Ritonavir capsules (Norvir®) require storage at 2-8°C (or must be used within 30 days if removed from refrigeration)[14] and must be taken alongside PIs. Lopinavir/ritonavir (Kaletra®), is the only co-formulated product available and does not require refrigeration[7].
- No new safety signals were identified in the treatment-naïve population of the ARTEMIS trial, and the safety and tolerability of darunavir appears similar to that seen with other boosted PIs[2]. The incidence of gastro-intestinal adverse effects was significantly lower with darunavir compared with lopinavir[10,11].
- The lipid profile of darunavir appears more favourable than lopinavir and some other PIs[4]. In the ARTEMIS study, increases in total cholesterol and triglycerides were significantly lower, and increases in LDL-cholesterol were numerically lower, with darunavir/ritonavir as compared to lopinavir/ritonavir[11]. Exploratory analyses of the ARTEMIS data suggest that a higher proportion of patients in the lopinavir/ritonavir group experienced elevations in total cholesterol and triglycerides[3]. Any reduced need for lipid-lowering therapy may potentially impact on polypharmacy issues and cardiovascular (CV) disease.

However, the proportions of patients taking lipid lowering therapy was similar in the trial at 96 weeks (7-8%)[11] and CV outcomes data are lacking.

- Darunavir and ritonavir are inhibitors of CYP3A4, and darunavir is contraindicated with drugs that are substrates of this enzyme and have a narrow therapeutic index[1]. The SPC should be consulted for full details of potential drug interactions.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue to consider is whether the additional benefits offered by darunavir over the relevant comparator(s) justify the additional costs and if so, whether the total budgetary impact of supporting the use of darunavir is acceptable (see section 9.0).

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8.2 Description and critique of the company's submission

The company's submission[3] describes a cost utility analysis of once daily darunavir 800mg/ritonavir 100mg compared with lopinavir 800mg/ritonavir 200mg per day, both in addition to a fixed background NRTI regimen of tenofovir DF 300mg/emtricitabine 200mg, as first-line treatment in treatment-naïve HIV-1 patients. A Markov model has been created, which describes six health states relating to patients with CD4 counts of >500, 351–500, 201–350, 101–200, 51–100 and 0–50 cells/mL, and a seventh, absorbing state of death. Patients may remain in, or move between the six states, or progress into the seventh state, based on their virological response to treatment (undetectable [viral load <50 copies/mL], partial suppression [detectable viral load but a minimum of a 1.0 $\log_{10}$ drop in viral load is achieved], and no suppression [< 1.0 $\log_{10}$ drop in viral load is achieved]). For each virological response category, the CD4 count is assumed to change via three sequential stages: an 'initial increase', followed by a 'stable/slow increase', followed by a period of 'decline'. Following first-line treatment failure, patients follow a treatment pathway of second-line treatment with once daily atazanavir/ritonavir plus an optimised background regimen (OBR), third-line treatment with raltegravir plus OBR, and fourth-line treatment with any one of a range of regimens used in highly pre-treated patients. Patients are assumed to remain on their fourth-line regimen until death[3].

First-line treatment efficacy is based on the 24 to 96 week data from the ARTEMIS trial[3,10,11]. This is used to estimate the duration of the three stages of CD4 cell count changes for each virological response category[3]. The key parameter driving model outputs is the duration of the CD4 stable/slow increase stage, which in the base case analysis is modelled to be three years longer for darunavir/ritonavir compared with lopinavir/ritonavir based on a non-statistically significant hazard ratio for time to virological failure. The model estimates that darunavir/ritonavir is dominant over lopinavir/ritonavir in the base case analysis and in all of the one-way sensitivity analyses that were conducted in the original submission. However, each of these analyses retained this assumed three years longer duration of CD4 stable/slow increase stage. The company has subsequently provided additional one-way sensitivity analyses that explore the impact of reduced durations of CD4 stable/slow increase stage with darunavir/ritonavir treatment, but which retain an advantage over lopinavir/ritonavir treatment.

In addition to the sensitivity analyses that were conducted, the company submission also describes a scenario analysis, in which atazanavir/ritonavir is modelled as the first-line comparator. In this analysis, the duration of the CD4 stable/slow increase stage is

assumed to be the same for both treatments and sensitivity analyses indicate that the model is very sensitive to several parameters. The health economic model was provided which allowed interrogation.

8.3 Population

The baseline characteristics of the modelled patients in the darunavir/ritonavir and the lopinavir/ritonavir arms are based on the ARTEMIS trial population (see Table 1 in Appendix 1A)[3].

8.4 Perspective and time horizon

The analysis was conducted from the perspective of NHS Wales. A lifetime horizon has been used in the base case analysis[3], and each model cycle is three months long[3]. No details are provided regarding the time point within each Markov cycle at which costs and benefits were assumed to occur (e.g. no half cycle corrections are discussed).

8.5 Comparator

Lopinavir/ritonavir is an appropriate comparator for the analysis, as discussed in section 7.1. Following first-line treatment failure, patients follow a treatment pathway consisting of second-line treatment with once daily atazanavir/ritonavir plus an OBR, third-line treatment with raltegravir plus OBR, and fourth-line treatment with any one of a range of regimens used in highly pre-treated patients. Patients are assumed to remain on their fourth-line regimen until death[3].

A supplementary analysis using atazanavir/ritonavir as the first-line comparator has been conducted. In this analysis, following first-line treatment failure, patients follow a treatment pathway consisting of second-line treatment with lopinavir/ritonavir plus an OBR.

8.6 Clinical inputs

8.6.1 Efficacy data

In the base case analysis, the number of patients in each of the health states at model entry and the transition probabilities for movement between the different health states are based on data derived from the ARTEMIS trial[10]. It should be noted that around 25% of patients in the ARTEMIS trial received lopinavir/ritonavir as a once daily regimen, rather than as the twice daily regimen currently licensed in Europe[2,7]. The CHMP considered that this may have resulted in some lopinavir/ritonavir recipients receiving sub-optimal doses, which may have contributed in part to some differences observed in some outcomes[2] (see section 6.1 and 7.2). The economic model uses data from the whole ARTEMIS trial population.

For each virological response category (undetectable, partial suppression, or no suppression) the CD4 count is assumed to change via three sequential stages: an 'initial increase', followed by a 'stable/slow increase', followed by a period of 'decline'. However, for the first three lines of therapy, treatment switching is driven by virological failure rather than CD4 cell count decline, due to the availability of viable treatment options at this point in the treatment pathway. Patients are assumed to remain on their fourth-line treatment until death[3].

For the supplementary analysis using atazanavir/ritonavir as the first-line comparator, a detailed literature search was conducted to identify relevant efficacy data[3]. Only randomised controlled trials that assessed atazanavir 300mg/ritonavir 100mg once daily in combination with tenofovir 300mg/emtricitabine 200mg in treatment-naïve patients were included in the search. Only one trial, the CASTLE study, met all inclusion criteria. This compared the atazanavir/ritonavir regimen against the same

lopinavir/ritonavir regimen as in the ARTEMIS trial. An indirect comparison of the CASTLE and ARTEMIS trials has been conducted using 24-week data. No indirect comparisons were presented for 48, or 96-week data. The analysis is reported to indicate that treatment with darunavir/ritonavir results in a numerically but not statistically significantly higher proportion of patients achieving complete viral responses compared with atazanavir/ritonavir (80.0% versus 76.9%)[3]. These proportions have been used in the same way as the darunavir/ritonavir-lopinavir/ritonavir comparison has in the base case analysis discussed below. However, in contrast to the base case analysis using lopinavir/ritonavir as the comparator, the duration of all the three CD4 cell count change stages for atazanavir/ritonavir is assumed to be the same as for darunavir/ritonavir[3].

8.6.1.1 Transition probabilities and stages of CD4 cell count changes

For the first-line treatments, the magnitude of the initial increase in CD4 cell counts, by virologic response category, were reportedly based on the means and standard deviations for the CD4 cell-count changes that were observed in the ARTEMIS trial up to 24 weeks. For the stable/slow increase in CD4 cell count stage, data between 24 and 96 weeks have been used. These mean increases and standard deviations in CD4 cell counts were reportedly used to construct normal distributions with which the transition probabilities for the different virological response categories for the CD4 initial increase and stable/slow increase stages were estimated. It was assumed that patients are uniformly distributed within each CD4 health state and that all achieve the mean CD4 cell count change[3].

For the decline in CD4 cell count stage, which occurs only for fourth-line treatment, a number of sources of data have been used and assumptions made. The CD4 cell count decline was estimated using an equation derived from a cohort study of untreated patients (the Multicenter AIDS Cohort Study, MACS)[15], and adjusted with data from 13 cohorts of patients who had failed on three classes of antiretrovirals but had HIV viral loads less than 10,000 copies/mL and remained on treatment (The PLATO Collaboration)[16]. By inputting the baseline viral load from patients in the ARTEMIS trial into the equation, the annual decline in CD4 count if this population had not received treatment is estimated. By inputting a viral load of 10,000 copies/mL into the equation, the annual decline in CD4 count for those patients who have failed on antiretrovirals but who remain on therapy (as in the PLUTO Collaboration cohorts) can be estimated. The difference in these annual rates of decline in CD4 count, divided by four, has been used in the model to estimate the rate of decline in CD4 count per three-month cycle for the 'decline stage'. This rate has been assumed to be the same for all three virological response categories[3]. The range of assumptions used to generate this estimate are not supported or further explored in the company submission and it is unclear how these may affect the outputs of the model. Sensitivity analysis on the rate of CD4 decline has been conducted.

Second and subsequent lines of therapy are all assumed to be equally efficacious, with efficacy data (mean and standard deviations for CD4 cell count changes), reportedly based on that observed for etravirine in the DUET trials[3].

8.6.1.2 Duration of CD4 change stages

For first-line treatments, the duration of the CD4 initial increase stage is 0.5 years, irrespective of virological response achieved, based on the rapid increase in CD4 cell counts observed in virological responders during the first 24 weeks of the ARTEMIS trial[3]. The duration of the CD4 stable/slow increase stage varies by virological response category. Based on current guidelines[4] and company sought expert opinion, those patients not achieving at least 1.0 $\log_{10}$ drop in viral load by week 24 are assumed to be switched to the next line of therapy, and so the duration of the stable/slow increase stage is assumed to be zero. For those achieving partial viral load suppression (viral load >50 copies/mL but in whom a minimum of 1.0 $\log_{10}$ drop in viral load is achieved), it is assumed that the stable/slow increase stage would be 0.5 years (resulting in a total time to treatment failure of 1.0 year), simply on the basis that this is a compromise between aggressive management of patients with incomplete virological response and maintenance on therapy for patients with a delayed complete response.

The estimated duration of the CD4 stable/slow increase stage is the key driver of the modelled differences between darunavir/ritonavir and lopinavir/ritonavir. In those who achieve a complete virological response at 24 weeks (viral load <50 copies/mL), the duration of the CD4 stable/slow increase phase is estimated based on the ARTEMIS trial data and additional data derived from a UK multi-centre cohort study that enabled assessment of time to treatment failure for various HAART regimens[17]. Analysis of this cohort study data indicates that the median time to treatment failure with first-line ritonavir-boosted PIs was 4.5 years between the years 1996 and 2002[17]. However, the patient cohort in this study will not have received PIs, NRTIs and NNRTIs that became available post-2002. This estimate of time to treatment failure with PIs would therefore appear subject to some uncertainty. Nonetheless, this time to treatment failure has been assumed to be the average across all virological response categories for lopinavir/ritonavir treatment (in combination with tenofovir DF 300mg/emtricitabine 200mg). The company submission states that a weighted average technique has been used to estimate the time to treatment failure specifically for those who have achieved complete virological response, based on the assumed durations of treatment for those achieving partial suppression and those not achieving at least a 1.0 $\log_{10}$ decrease in viral load. The resultant median lopinavir/ritonavir treatment duration for those who achieve a complete virological response is estimated as being approximately 5.5 years, and the duration of the CD4 stable/slow increase stage is 5.5 years less the 0.5 years assumed for the CD4 initial increase stage, i.e. 5.0 years[3].

In relation to the CD4 stable/slow increase stage for darunavir/ritonavir treatment, the company submission states that this should be assumed to be longer than for lopinavir/ritonavir due to improved adherence with once daily dosing and its superior tolerability profile[3]. Additional commercial in confidence data was also provided regarding time to virological failure. The resulting hazard ratio was used to adjust the lopinavir/ritonavir treatment duration and duration of CD4 stable/slow increase estimates. The resultant treatment duration for darunavir is modelled as 8.5 years, and the duration of the CD4 stable/slow increase is modelled as 8.0 years, i.e. an increase of three years over lopinavir/ritonavir. It is worth noting that discontinuations due to virological failure in the ARTEMIS trial at 96 weeks were very low in both treatment arms (3/343 patients on darunavir/ritonavir, 8/346 patients on lopinavir/ritonavir)[11], and it should be considered that a proportion of the lopinavir/ritonavir recipients received a potentially sub-optimal once daily regimen[2] (although the analysis that generated the hazard ratio was confined to those who had achieved complete virological response at 24 weeks). One-way sensitivity analyses indicate that the model is most sensitive to the duration of the CD4 stable/slow increase stage. In the original submission, each of the one-way sensitivity analyses that were conducted around the duration of the CD4 stable/slow increase stage still maintained a three year difference in favour of darunavir

treatment[3]. Supplementary one-way sensitivity analyses exploring the impact of a reduced duration of the CD4 stable/slow increase stage have subsequently been provided by the company.

The duration of the CD4 decline stage is zero for the first three lines of treatment, as patients are assumed to switch to the next line of treatment based on virological response rather than CD4 decline. For those on the fourth (last) line of treatment, the duration of the CD4 decline stage is assumed to be equal to the remaining life time of the patient[3].

8.6.2 HIV and non-HIV mortality

The model allows for patients dying from HIV and non-HIV causes. Annual HIV-related mortality rates were taken from a cohort of patients followed up via the EuroSIDA database[18], transformed where necessary to the match the health states of the model defined by CD4 cell count, and converted to provide three month probabilities of death[3]. Non-HIV annual mortality rates were calculated from Welsh all-cause mortality rates. As all-cause mortality rates include small numbers of HIV-related deaths, these were subtracted from all-cause deaths based on the relative risk of mortality for HIV patients with CD4 counts >200 cell/mm^3 compared with the general population in a Danish cohort study[19]. Three age ranges are considered in the model (15–39 years, 40–64 years and 65-plus) and weighted average non-HIV death rates were calculated for these, transformed into three month rates[3].

8.6.3 Adverse events

Treatment-related adverse events have not been incorporated into the model. As the incidence of grade 2-4 adverse events thought to be possibly related to treatment was lower with darunavir/ritonavir treatment compared with lopinavir/ritonavir in the ARTEMIS trial[2] this may be considered a conservative approach that favours the comparator in the base case analysis. In addition, increases in total cholesterol, triglycerides and HDL-cholesterol were significantly lower, and increases in LDL-cholesterol were numerically lower, with darunavir/ritonavir as compared to lopinavir/ritonavir[11] (see section 6.2 and 7.2).

8.6.3 Utility weights

Utility values for each health state of the model were obtained from a cost-effectiveness analysis of lopinavir/ritonavir versus nelfinavir as a first-line antiretroviral regimen[20]. This analysis used EQ5D-derived utility values obtained from around 21,000 clinical trial participants. It is unclear how long ago or what disease state these trial participants were in when these utility values were obtained and, given the advances in the treatment of HIV that have been achieved since the first antiretroviral agents became available, it is possible these utility values are outdated. Sensitivity analysis has been conducted on these utility values.

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

Drug costs in the model relate to antiviral costs, which are based on the recommended daily doses and unit costs listed in the British National Formulary (BNF) prices[21]. The daily cost of darunavir 800mg, based on two 400mg tablets, is stated to be £9.92 in the company submission[3]. A weighted average daily cost has been calculated for each modelled combination regimen, based on the proportion of patients using each drug in that regimen. The proportions of patients using each drug is reportedly based on that observed in the ARTEMIS trial and a range of other key trials of other regimens. These are used to estimate three-month weighted costs.

8.7.2 Adverse event costs
No costs specific to adverse events are included in the model.

8.7.3 Other resource use and costs
Non-drug costs are based on commercial in confidence data which is an update to a previous study published in 1996[22]. This provides mean three-month per patient costs (2006/7 prices) by CD4 cell count range. The resource use and costs incorporated in this study remain commercial in confidence with few details provided.

8.8 Discounting
Costs and outcomes are discounted at 3.5% per annum, which is the preferred discount rate. Discount rates of 0-6% per annum have been explored in sensitivity analysis[3].

8.9 Base-case results
8.9.1 Base-case analysis: darunavir/ritonavir versus lopinavir/ritonavir
In the base-case analysis, darunavir/ritonavir is estimated to be more effective than lopinavir/ritonavir (life time QALYs 14.248 versus 13.959, gain of 0.289 QALYs) and less expensive (life time costs £223,953 versus £228,695, cost saving of £4,742) in treatment-naïve patients (i.e. darunavir/ritonavir dominates lopinavir/ritonavir). Drug costs represent the majority of the total costs and are the greatest source of cost savings.

8.9.2 One-way sensitivity analyses
Several one-way sensitivity and scenario analyses have been conducted across several parameters using a range of values, including the 95% CI where appropriate. In all of the analyses in the original submission darunavir/ritonavir remained dominant over lopinavir/ritonavir[3]; however, these retained an assumed three-year advantage in the duration of the CD4 slow/stable increase stage for darunavir/ritonavir compared with lopinavir/ritonavir

In the base-case analysis, the duration of the CD4 stable/slow increase stage for darunavir/ritonavir treatment was derived from exploratory analyses of the time to virological failure between darunavir/ritonavir and lopinavir/ritonavir over 96 weeks in those subjects who had achieved complete virological response at 24 weeks in the ARTEMIS trial. Additional commercial in confidence data was also provided. From this data, the impact of the uncertainty in the hazard ratio and consequently the duration of the CD4 slow/stable increase stage, was not explored adequately in the original submission. Subsequently, the company has provided supplementary one-way sensitivity analyses that explore the impact of reducing the additional duration of the CD4 stable/slow increase stage for darunavir/ritonavir. When this additional duration is reduced to two years, darunavir/ritonavir remains dominant over lopinavir/ritonavir, but when the duration is reduced to six months, the model outputs switch from darunavir/ritonavir being the dominant strategy to having an incremental cost per QALY gained of £3,405 compared with lopinavir/ritonavir. When the additional duration is reduced to three months, the incremental cost per QALY gained increases several-fold to £26,780. This highlights the sensitivity of the model to this parameter. An analysis in which there is no assumed advantage in the duration of the CD4 slow/stable increase stage for darunavir/ritonavir compared with lopinavir/ritonavir has not been presented.

Other parameters to which the base case model is most sensitive are the rate of CD4 cell count decline, which applies only to the fourth line treatment, and the relative risk of non-HIV related mortality. When different time horizons, discount rates, starting CD4 cell counts, age distributions and sex distributions were explored the model still

estimated darunavir/ritonavir to dominate lopinavir/ritonavir[3]. However, these analyses retain the three-year advantage in the duration of the CD4 slow/stable increase stage for darunavir/ritonavir compared with lopinavir/ritonavir. Two-way sensitivity analyses of the assumed duration of the CD4 stable/slow increase stage and the tested parameters, might have revealed important changes in the ICER resulting from their uncertainty.

8.9.3 Probabilistic sensitivity analysis

Distributions were fitted to several key parameters within the model. A sample of 1,000 patients has been simulated to generate a cost effectiveness acceptability curve. This indicates that the probability of darunavir being cost effective at a willingness to pay threshold of £20,000 is 87.8%, and at £30,000 is 88.7%[3]. However, the issue of the uncertainty in the duration of CD4 stable/slow increase stage for darunavir/ritonavir treatment, is not addressed by this probabilistic analysis.

8.10 Scenario analysis: darunavir/ritonavir versus atazanavir/ritonavir

In this analysis, based on an indirect comparison of efficacy data, and an assumed duration of the CD4 slow/stable increase stage of eight years for both darunavir and atazanavir, darunavir/ritonavir is estimated to be more effective than atazanavir/ritonavir (life time QALYs 14.248 versus 14.224, gain of 0.024 QALYs) and less expensive (life time costs £223,953 versus £224,849, cost saving of £897) in treatment-naïve patients (i.e. darunavir/ritonavir dominates lopinavir/ritonavir). Drug costs represent the majority of the total costs and are the greatest source of cost savings. However, these results should be interpreted with caution.

One-way sensitivity analyses indicate that this model is very sensitive to several parameters. The rate of CD4 initial increase switches the model outputs from darunavir/ritonavir being dominant over atazanavir/ritonavir to having an incremental cost per QALY gained of over £100,000 when explored within the range of its 95% CI. The rate of CD4 slow increase produces an incremental cost per QALY gained of over £50,000. Several other parameters when explored within their 95% CIs yield positive incremental cost effectiveness ratios[3]. The company submission states that these sensitivities reflect the small differences in costs and effects that have been modelled[3]. It is noteworthy that a probabilistic sensitivity analysis was not presented for this scenario analysis, and so the combined impact of the uncertainty in all key parameters, and the probability of cost effectiveness at specific thresholds of willingness to pay per QALY gained, cannot be assessed.

The company has subsequently provided additional one-way sensitivity analyses in which the assumed duration of the CD4 slow/stable increase stage is reduced to 5.25 years for both darunavir and atazanavir, In these analyses, the rate of CD4 initial increase switches the model outputs from darunavir/ritonavir being dominant over atazanavir/ritonavir to having an incremental cost per QALY gained of £30,597 when explored within the range of its 95% CI. Similarly, the rate of CD4 slow increase produces an incremental cost per QALY gained of £34,972. This new modelled scenario, using a reduced duration of the CD4 slow/stable increase stage for both darunavir and atazanavir, results in more favourable results for the one way sensitivity analyses, but still demonstrates the sensitivity of the model to these key parameter assumptions.

8.11 Review of published evidence on cost-effectiveness

Standard literature searches did not identify any published cost effectiveness analyses of the use of ritonavir-boosted darunavir in treatment-naïve patients.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

The number of treatment-naïve patients predicted to be eligible for treatment with a PI has been estimated using historical and recent epidemiological data from National Public Health Service for Wales (NPHSW) and Health Protection Agency (HPA). However, there appears to be significant uncertainty in the resultant estimates which, when combined with company's anticipated rates of uptake, warrants cautious interpretation in the estimated budget impact.

9.2 Perspective and time horizon

The analysis considers direct costs from the perspective of NHS Wales over a five year period (2009 to 2013)[2].

9.3 Data sources

9.3.1 Incident and prevalent cases

The company submission refers to NPHSW and HPA data to estimate the prevalence of HIV infection in Wales in 2008. It is reported in the submission that a linear regression model has been fitted to the number of new diagnoses recorded between 2001 and 2007 and that this equation has been used to estimate the number of new cases expected each year. Assuming a stable mortality rate of 1.3%, the company estimates that the net prevalence of HIV in Wales in 2008 would be 1,639 cases[3]. The actual derivation of this figure is not immediately clear, and contrasts with another estimate in the company submission of 1,280 patients living with HIV in Wales at the end of June 2008[3].

The linear regression model has reportedly been used to estimate the number of new diagnoses expected over the next five years[3]. This predicts a rise in new cases of around 19 year on year. Data from the NPHSW indicate that there were 192 new diagnoses in Wales in 2007[23]. The company submission states that in 2008 there would be 192 new cases, rising to 296 in 2013. The derivation of the 2008 incidence figure is unclear and contrasts with 133 new diagnoses reported by HPA in 2008[24]. The incidence and prevalence figures reported in the company submission would therefore appear to subject to some uncertainty.

The company submission notes that not all patients would receive treatment and care. It assumes that 95.8% of the predicted numbers of patients would receive care, reportedly based on HPA data from 2004[25], although the source of that figure is unclear from the cited reference. Applying this proportion to the 2008 prevalence estimate yields 1,571 patients receiving care in Wales in 2008[3]. For reference, this compares with 1,009 patients reported to be receiving care in Wales in 2007[24]. The company submission then states that, of those patients been seen for care, 28.7% (451 patients) would be antiretroviral treatment-naïve and, of those, 68% (307 patients) would be started on antiretroviral treatment at any given year. The source of these estimates is not stated or clear. Given the above uncertainties with the estimated prevalence and incidence figures, and the assumed number of patients who are treatment naïve and would start treatment, these figures should be interpreted with caution.

9.3.2 Projected rate of adoption and market share

It is assumed in the submission that, of those previously untreated patients who would be started on antiretroviral treatment each year (estimated by the company as 307 patients in 2008), a third will be eligible for treatment with PI (102 patients in 2008). Of these, 10% are anticipated to be treated with darunavir in 2008 (10 patients). The number of previously treatment-naïve patients anticipated to be treated with darunavir

in 2009 is estimated to be 11, rising to 52 in 2013. Given the above uncertainties, these figures should be interpreted with caution.

9.3.3 Costs and resource use

The ritonavir-boosted PI costs are based on BNF-listed prices[21] for the usual recommended doses. The weighted average annual cost of treatment with ritonavir-boosted PIs other than darunavir is reported to have been estimated using UK market share data (no further details provided). This is estimated to be £3,815.35 per patient, compared with an annual cost of ritonavir-boosted darunavir of £4,015 per patient[3]. It is assumed implicitly that patients would receive the same backbone treatments and so the costs of other antiviral agents in each patient's regimen are not included in the analysis.

The company submission states that drug acquisition costs are similar for the PIs and highlights non-antiviral treatment cost savings due to reduced medical resource use with the use of darunavir/ritonavir compared with lopinavir/ritonavir. However, these were generally outweighed by the antiviral drug cost differences (see section 8.9 and 8.10).

9.4 Results

The company estimates the net budget impact, based on drug acquisition costs only, as in Table 2. Given the range of uncertainties in the estimates of the number of patients eligible for treatment, these figures should be interpreted with caution.

Table 2. Company-estimated budget impact of the use of darunavir/ritonavir in treatment-naïve patients[3]

	2009	**2010**	**2011**	**2012**	**2013**
No. patients anticipated to be eligible for darunavir treatment	11	19	28	39	52
Weighted average costs of PIs without darunavir	£41,969	£72,492	£106,830	£148,799	£198,398
Costs using darunavir	£44,165	£76,285	£112,420	£156,585	£208,780
Net budget impact	**£2,196**	**£3,793**	**£5,590**	**£7,786**	**£10,382**

9.5 Sensitivity / scenario analysis

No sensitivity analysis has been performed around the budget impact analysis.

9.6 Comparator costs

The 28-day costs of ritonavir-boosted PIs that are licensed in treatment-naïve patients are listed in Table 3, based on usual doses recommended in MIMS (September 2009)[26].

Table 3. 28-day costs of selected ritonavir-boosted PIs

PIs	Example dose	Approximate 28-day cost[26]
Atazanavir	Atazanavir 300mg / ritonavir 100mg od	£315
Lopinavir/ritonavir	Lopinavir 400mg / ritonavir 100mg (as Kaletra®) bd	£287
Fosamprenavir	Fosamprenavir 700mg ritonavir 100mg bd	£319
Saquinavir	Saquinavir 1000mg / ritonavir 100mg bd	£302
Darunavir (as 400mg tablets)	Darunavir 800mg / ritonavir 100mg od	£309
od= once daily, bd = twice daily		

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- BHIVA issued guidelines on the treatment of HIV-1 in adults in 2008[3], as discussed in section 3.0 and throughout the ASAR.
- HPA, in collaboration with National Public Health Survey for Wales, conduct an annual survey (SOPHID) of all patients seen for HIV-related treatment or care[24].
- Darunavir will be initiated by specialists and would not currently be deemed suitable for shared care.

10.2 Previous AWMSG advice

- Etravirine (Intelence®▼) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infected, antiretroviral treatment-experienced adults in combination with a boosted protease inhibitor and other antiretroviral medicinal products. Treatment should be initiated by a specialist in accordance with BHIVA guidelines; August 2009[27].
- Maraviroc (Celsentri®▼) is recommended as an option for use within NHS Wales for the treatment of treatment-experienced adults infected only with CCR5-tropic HIV-1, in accordance with BHIVA guidance; April 2009[28].
- Efavirienz/emtricitabine/tenofovir DF (Atripla®) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in adults with virological suppression to HIV-1 RNA levels of <50 copies/mL on their current combination antiviral therapy for more than three months and in accordance with current BHIVA guidance; February 2009[29].
- Atazanavir (Reyataz®) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-naïve patients, in accordance with BHIVA guidance; December 2008[30].
- Atazanavir (Reyataz®) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-experienced patients, in accordance with BHIVA guidance; December 2008[31].
- Raltegravir (Isentress®▼) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in treatment-experienced adults in accordance with BHIVA guidance; October 2008[32].

- Fixed-dose abacavir and lamivudine (Kivexa®) is recommended as an option for use within NHS Wales in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents from 12 years of age. Use should be in accordance with BHIVA guidance; October 2008[33].
- Emtricitabine (Emtriva®) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral agents for use in treatment-naïve patients in line with current BHIVA guidelines; June 2007[34].
- Emtricitabine/tenofovir DF (Truvada®) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults who are treatment-naïve and in line with current BHIVA guidelines; June 2007[35].
- Darunavir (Prezista®▼) is recommended for the treatment of HIV-1 infection in highly pre-treated adults who have failed more than one regimen containing a PI, and where resistance profiling suggests it is appropriate, in accordance with BHIVA guidelines; August 2007[36].
- Tipranavir (Aptivus®▼) is recommended for the treatment of HIV-1 infection, only for the treatment of highly pre-treated adult patients who have failed multiple PIs, and where resistance profiling suggests it is appropriate, in accordance with BHIVA guidelines; August 2007[37].
- Enfuvirtide (Fuzeon®) is recommended as an option for use for the treatment of patients with HIV-1, with restrictions; May 2004[38].

10.3 Ongoing studies

- The company submission[3] indicates that the 144-week results of the ARTEMIS trial are anticipated to be available in the next 6-12 months.
- A trial to assess the efficacy and safety of darunavir 800mg/ritonavir 100mg once daily as monotherapy in treatment-naïve patients (MONET study, unlicensed indication) is ongoing, and 48 weeks results are available.
- Two trials of darunavir in treatment experienced patients (ODIN and GRACE studies) are also ongoing with results anticipated in the next 6-12 months[3].

10.4 Patient organisation information

A patient organisation submission by The Terrence Higgins Trust was provided to members.

10.5 Medical expert / Clinical expert summary

Medical / clinical expert views were provided to members.

GLOSSARY

Incidence:
The rate at which new cases occur in a population during a specified period[39].

Prevalence:
The proportion of a population that are cases at a point in time[39].

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Appendix 1. Additional Clinical Information

Table 1A. ARTEMIS trial: Darunavir/ritonavir versus lopinavir/ritonavir in ART-naïve HIV-1 infected patients

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (Darunavir/r versus LOP/r)
48 week study results						
2,3,10 ARTEMIS study	Randomised, open-label, phase III, multinational, non-inferiority trial	691 patients randomised, of which 689 treated	HIV-1 patients aged ≥18 years; ART-naïve; HIV RNA ≥5000 copies/mL; Chronic, stable hepatitis B/C allowed if didn't require treatment	Mean age: 35.4 years Males: 70% White: 42% Black: 22% Hispanic: 22% Other:14% Mean time since diagnosis: 2.5 years Mean HIV RNA: 4.85 log_{10} copies/mL (34% ≥ 100,000 copies/mL) Median CD4: 225 cells/mm^3 (38% <200 cells/mm^3) CDC Class A: 64% B: 27% C: 9% Chronic hepatitis B and/or C: 13%	Darunavir/r od (n=343) versus LOP/r per day* (n=346) Each in combination with fixed dose combination tenofovir DF 300mg/ emtricitabine 200mg od	**Primary endpoint (PP analysis):** Proportion with **HIV RNA <50 copies/mL at week 48** (measured as TLOVR): 84% versus 78% (difference 5.6%, 95% CI: -0.1 to 11) Non-inferiority criterion met† Superiority not achieved (p=0.062) **ITT analysis:** 83.7% versus 78.3% (difference 5.3%, 95% CI -0.5 to 11.2) Non-inferiority criterion met† **By baseline stratification factors (PP analysis):** HIV RNA <100,000 copies/mL (n=452): 86% versus 85%; NS HIV RNA ≥100,000 copies/mL (n= 237): 79% versus 67%; p<0.05 CD4 cell count <50 copies/mm^3 (n=60): 77% versus 67%; NS CD4 cell count 50-200 copies/mm^3 (n=229): 80% versus 71%; NS CD4 cell count ≥200 copies/mm^3 (n=400): 87% versus 84%; NS **Secondary endpoints at 48 weeks:** Proportion with **HIV RNA < 400 copies/mL at week 48**: 87.8% versus 85.3% (difference 2.5%, 95% CI: -2.6 to 7.6) **Mean change from baseline HIV RNA**: -2.77 versus -2.65 log_{10} copies/mL (difference -0.09, 95% CI : -0.26 to 0.07) **Mean change from baseline CD4 count**: 154 versus 161 cells/mm^3 (difference -7, 95% CI: -27 to 13) **Median change from baseline CD4 count**: 137 versus 141 cells/mm^3

96 week interim study results						
3,11 ARTEMIS study	-	-	-	-	-	Proportion with **HIV RNA < 50 copies/mL (ITT analysis)**: 79% versus 71% (difference 8.3%, 95% CI 1.8 to 14.7) Superiority achieved (p=0.012) By baseline stratification factors (ITT analysis): HIV RNA <100,000 copies/mL: 81% versus 75%; NS HIV RNA ≥100,000 copies/mL: 76% versus 63%; p=0.023 CD4 cell count <200 copies/mm^3: 79% versus 65%; p=0.009 CD4 cell count ≥200 copies/mm^3: 79% versus 75%; NS **Median change from baseline CD4 count**: 171 versus 188 cells/mm^3
ART = antiretroviral; CDC = Centre for Disease Control; Darunavir/r od = Darunavir 800mg/ritonavir 100mg once daily; ITT analysis = intention to treat analysis; LOP/r = Lopinavir 800mg/ritonavir 200mg per day; NS = not statistically significant; PP analysis = per protocol analysis; TLOVR = Time to loss of virological response; * = approx. 23% received LOP/r as 800mg/200mg once daily regimen (unlicensed regimen in Europe) at some point in the study, and 77% as 400mg/100mg twice daily regimen only (licensed regimen in Europe)[2,10]; † = non-inferiority met if lower limit of 95% CI for the difference in virological response did not exceed -12%. Was pre-specified that superiority was to be assessed if non-inferiority was achieved.						