All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Darunavir (Prezista®)
Tibotec, a division of Janssen-Cilag

Advice No: 0907 – August 2007

Recommendation of AWMSG

Darunavir (Prezista®) should be recommended within NHS Wales for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adults who have failed more than one regimen containing a protease inhibitor (PI), and where resistance profiling suggests it is appropriate.

Use should be in accordance with the British HIV Association (BHIVA) guidance

Darunavir (Prezista®) is not presently recommended for shared care.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

Date: 15th August 2007

The recommendation of AWMSG is:

- Darunavir (Prezista®) should be recommended within NHS Wales for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adults who have failed more than one regimen containing a protease inhibitor (PI), and where resistance profiling suggests it is appropriate.

- Use should be in accordance with the British HIV Association (BHIVA) guidance.

- Darunavir (Prezista®) is not presently recommended for shared care.

2.0 PRODUCT DETAILS

3.1 Licensed indication:
Darunavir (Prezista®), 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).

This indication is based on week 24 analyses of virological and immunological response from two controlled dose range finding Phase II trials and additional data from uncontrolled studies (see section 5.1 of the Summary of Product Characteristics).

In deciding to initiate treatment with darunavir co-administered with 100mg ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide its use[1,2].

2.2 Dosing:
Darunavir is available as film-coated 300 mg tablets. The recommended dosage is 600mg twice daily (bd) taken with ritonavir 100mg bd and with food. The recommended dosing interval is 12 hours. If a dose is missed by more than six hours the missed dose should not be taken and the patient should resume the usual dosing schedule[1].

2.3 Market authorisation date:
February 2007[2]

2.4 UK Launch date:
February 2007

3.0 DECISION CONTEXT

Most people infected with HIV-1 who start highly active antiretroviral therapy (HAART) will experience good virological responses to treatment. However, due to a range of factors, including poor adherence, tolerability problems, inadequate drug concentrations, and pre-existing or newly developed antiretroviral resistance, virological responses may fail over time. Subsequent regimens may be progressively less likely to produce a durable virological response and the worry is that available options for treatment may become limited or exhausted for some patients[3].

Recent surveillance data from the Health Protection Agency[4] indicate that resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTI) has decreased in recent years. As of the end of 2004, the prevalence of NRTI and NNRTI resistance was similar at around 4.5%, and for PIs it was 2.1%[4]. Nonetheless, there remains a proportion of highly pre-treated patients who may not achieve the goals of undetectable and durable HIV plasma viral load suppression and immunological improvement[5].

The British HIV Association guidelines[5] emphasise that, in highly pre-treated HIV-1 infected patients, therapy has to be tailored based on a range of factors, including their individual prior antiretroviral treatment histories and resistance profiles. A new regimen that includes at least two, but preferably three, active agents should be constructed.

There is, therefore, a need for new antiretroviral agents that are active against HIV-1 where other agents are no longer.

Darunavir is a new PI that has recently been licensed for use (boosted with ritonavir) in combination with other antiretroviral agents in highly pre-treated patients who have failed on two or more previous PI regimens. The marketing authorisation was granted on the basis of limited comparative data, especially in respect of the safety profile of darunavir[2]. Tipranavir (Aptivus®), another new PI, is also licensed for use in highly pre-treated patients with virus resistant to multiple PIs[6]. There are no direct comparative data for these agents.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness:

The marketing authorisation for darunavir is based mainly on data obtained from two ongoing phase IIb clinical trials, POWER 1 & 2. On the basis of these limited data, darunavir would appear to offer an efficacious treatment option to highly pre-treated patients who otherwise might have limited or no treatment options. The virological and immunological responses observed at 24 weeks are clinically and statistically superior to those obtained with the control PI regimens used in the trials, and on the basis of 48 week data these responses appear to be sustained.

It should be noted that tipranavir, another PI recently licensed for use in highly pre-treated patients, was not included as a control PI and there are no direct comparative data for darunavir and this agent.

The available data appear to indicate that darunavir has a comparable safety profile with that of the PI class in general, but further data are required to fully characterise its safety profile. POWER 1 & 2 will each eventually provide 144 weeks of follow-up data and a phase III trial in this patient population is also ongoing.

4.2 Review of the evidence on cost-effectiveness:

As with many new drugs, there is a lack of long-term follow up data on which to base the economic modelling for darunavir. The economic model presented in the company submission therefore relies upon a number of assumptions.

The incremental cost per QALY estimated for darunavir in the base case analysis falls within what might reasonably be considered to be cost-effective and the sensitivity analyses that were conducted would appear to support this.

On this basis, and the fact that darunavir is licensed for use in patients who have limited treatment options available to them, WMP is of the opinion that darunavir, when used within its licensed indication, may be a cost-effective use of healthcare resources.

5.0 LIMITATIONS OF DECISION CONTEXT

Darunavir is currently unlicensed in children. Results on the safety and efficacy of darunavir from the POWER trials are short-term (up to 48 weeks). Follow up data from these trials are required to assess long-term safety and efficacy.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

The company submission[7] included the available results from two ongoing, phase IIb trials (POWER 1 and POWER 2), which were the main efficacy studies supporting the licence application for darunavir. Additional data from an ongoing, open-label, uncontrolled study (POWER 3) are included in the safety analysis (section 6.2). Combined 48-week results of the POWER 1 and 2 studies have subsequently been published[8].

6.1.1 POWER 1 & 2 trials

The POWER 1 (n=318) and POWER 2 (n=317) trials are being conducted in adult HIV-1 patients who, at initial screening, had plasma HIV-1 RNA >1000 copies/ml, were receiving a PI-containing regimen, were "three-class experienced" (i.e. had previously received at least one PI, two or more nucleoside reverse transcriptase inhibitors [NRTI], and at least one non-nucleoside reverse transcriptase inhibitor [NNRTI] for at least three months each), and had at least one primary PI mutation. Prior to randomisation, investigators selected for each patient a PI based regimen and an optimised background regimen (OBR) consisting of two or more NRTIs, with or without enfuvirtide, based on screening resistance data and prior antiretroviral therapy history. At baseline, patients were randomised to receive one of four darunavir/ritonavir regimens (400/100mg once daily [od], 800/100mg od, 400/100mg bd or 600/100mg bd) or their investigator chosen PI regimen (the control group), plus their OBR[2,7,8].

Both studies consisted of a 24 week dose-finding period, followed by a 120 week continuing treatment period. The studies were partially blinded during the dose finding period only; patients and investigators knew which treatment had been received, but not the actual doses. The original primary endpoint was change in viral load from baseline. However, following discussions with the regulatory authorities and pre-specified interim analyses at 16 and 24 weeks (which demonstrated that the 600/100mg bd darunavir/ritonavir regimen was significantly superior to the other darunavir regimens without increased toxicity), the primary endpoint was changed to virological response, defined as $\geq$ 1.0 $\log_{10}$ decrease in viral load versus baseline at week 24. This endpoint is more consistent with that used in recent trials of other agents (e.g. the RESIST trials of tipranavir used this outcome measure as the primary endpoint at 48 weeks[9]). Although it is a surrogate outcome, it is recognised as an appropriate measure of efficacy in this setting[10]. From week 24 onwards, all darunavir recipients received the 600/100mg bd regimen and the control group continued with their investigator chosen regimen[2,7,8].

Baseline characteristics were generally similar between groups within trials and between trials; however, in POWER 1, patients with hepatitis B or C were permitted (compared with POWER 2 which excluded these patients) and the European Public Assessment Report (EPAR) notes that a higher proportion of patients in the control group were co-infected with hepatitis B or C than in the darunavir group (21% vs. 12%)[2]. In addition, the POWER 2 patient population had a more advanced disease state than the POWER 1 population (lower baseline CD4+ counts, longer duration of infection and treatment experience)[2,7].

The 24-week and 48-week results of POWER 1 and 2 are summarised in table one for patients who received the darunavir/ritonavir 600/100mg regimen throughout and the control PI regimens[2,7,8]:

Table one. 24 and 48-week efficacy results from POWER 1 and 2

Efficacy Parameter	POWER 1 24-week data		POWER 2 24-week data		POWER 1 & 2 combined 24-week data		POWER 1 & 2 combined 48-week data	
	Darun/Rit 600/100mg n=65	Control PI n=63	Darun/Rit 600/100mg n=66	Control PI n=61	Darun/Rit 600/100mg n=131	Control PI n=124	Darun/Rit 600/100mg n=110	Control PI n=120
Primary endpoint								
% achieving ≥ 1.0 log10 decrease in viral load vs. baseline	77	29	64	13	70*	21	61*	15
					Absolute difference 49%, NNT=2		Absolute difference 46% (95%CI 35–57%) NNT=2	
Key secondary endpoints								
% achieving viral load <50 HIV-1 RNA copies/ml	52	16	38	8	45*	12	45*	10
Mean (SD) change from baseline in CD4+ cell count ($x10^6$ cells/l)	118 (136.2)	24.7 (106.5)	67.3 (79.1)	9.7 (92.2)	92.4* (113.6)	17.3 (99.6)	101.5* (126.9)	18.8 (102.5)
*P<0.0001 for Darun/Rit vs. Control PI ; all other comparisons P<0.001; NNT=number needed to treat with Darun/Rit vs. Control PI, rounded to nearest whole number								

These data were analysed on an intention-to-treat basis and indicate that the darunavir regimen was significantly superior to the control PI regimen for the primary (NNT=2) and secondary endpoints at 24 weeks. The 48-week data suggest that these effects are durable (NNT for primary endpoint = 2). Although not presented in the company submission, the EPAR contains available data on these endpoints up to week 72[2], which indicate that virologic response (≥ 1.0 $\log_{10}$ drop in viral load) tended to decrease overtime, but the response was sustained for up to at least Week 72 for the secondary efficacy endpoint of HIV-1 RNA < 50 copies/ml. Published 48-week data indicate that 46% of patients receiving the darunavir regimen and 81% of patients receiving control PIs never achieved a confirmed HIV-1 RNA < 50 copies/ml[8].

Health-related quality of life (HRQoL) was assessed in the POWER 1 & 2 trials using a validated tool, the Functional Assessment of HIV Infection Instrument (FAHI). The company submission provides results based on available 48 week data for the darunavir/ritonavir 600/100mg groups vs. the control PI groups. These indicate that darunavir significantly improved overall HRQoL, and the physical and emotional subscales of the FAHI, from baseline. In contrast, the control PI groups experienced a decline in overall HRQoL over the same period[7]. It is unclear how many patients these data are based on and the recently published combined 48 week data[8] does not include HRQoL data.

The 48 week discontinuation rate for darunavir was lower than for the control PI groups (combined results 21% vs. 81% respectively, no p-value provided)[8]. The main reasons for discontinuation were adverse events/HIV events for darunavir (9% vs. 5% for control PI) and virological failure for the control PI group (67% vs. 8% for darunavir)[8].

6.1.2 Points to note from the POWER 1 & 2 trials:

- It is recognised that double blinding can be difficult to achieve in this trial setting[10]. Although the primary endpoint was changed to response rate, this is considered a more conservative endpoint than change in $\log_{10}$ viral load and the results are considered robust[2].
- These were multinational trials, including patients from the UK. Patients in these trials are likely to adequately reflect the highly pre-treated patient population in Wales. At baseline, the mean duration of infection was in excess of 11 years and over 90% of the trial populations had previous experience of treatment with ≥2 PIs, ≥1 NNRTI and ≥4 NRTIs[11]. The median number of primary PI mutations was 3 (range: 0-5), and the median number of PI resistance-associated mutations was 8 (range: 0-12).
- The control PI group is a suitable comparator for darunavir in these trials, and the methods of establishing the investigator chosen OBRs were in line with current clinical practice[2].
- Tipranavir, another agent that is also licensed for use in highly pre-treated HIV-1 adults[6], was not included in the control group as it was not available at the time of enrolment.
- NNRTIs were, appropriately, not allowed in any groups in the trials as resistance to one NNRTI is nearly always associated with resistance to all NNRTIs [2]. The OBR for the control groups had to contain at least one PI and fusion inhibitor enfuvirtide was allowed in any group. Having at least one PI in the regimen to which the virus was susceptible was an important determinant of response. Also, responses to enfuvirtide were improved when patients were on at least one antiretroviral treatment to which the virus was susceptible. Similar numbers of the darunavir and control PI recipients received ritonavir as a PI booster (100% vs. 98%), and enfuvirtide (40–45%)[2].
- The difference in response rates for the primary endpoint and the secondary endpoint of viral load was maintained across all subgroup analyses[8].
- The POWER trials are ongoing and will eventually provide data for up to 144 weeks of follow up for darunavir against control PIs.
- 48 week data provided is based on cleaned and validated patient data only and therefore not all patients have been included in this interim analysis.

6.2 Safety:

The EPAR for darunavir notes that, in many studies, the dose of darunavir used was generally lower than the recommended dose, and the lack of head-to-head phase III studies versus comparators in similar therapeutic indications precludes a definitive conclusion related to the safety profile of darunavir compared to other PIs[2]. It is in this context that the current safety data for darunavir should be interpreted.

Based on the limited data that are available from the POWER 1, 2 & 3 studies, the safety and adverse event profile of darunavir appears to be similar to that observed with other PIs[2,7]. As control PI recipients discontinued therapy earlier than darunavir recipients (due mainly to virological failure), the possibility of experiencing adverse events was elevated over time for darunavir compared with control PIs. Therefore, the rate of adverse events per 100 patient years of exposure was calculated.

From the POWER 1, 2 and 3 studies, the most frequently reported adverse events (per 100 patient years of exposure) for darunavir vs. control PIs (from POWER 1 and 2) were diarrhoea (23.0 vs. 46.7 for control PIs), nausea (18.4 vs. 21.3), nasopharyngitis (17.8 vs. 17.3) and headache (16.5 vs. 33.3). Only for herpes simplex was the rate distinctly higher with darunavir (11.0 vs. 2.7)[12]. In the phase IIb studies, any liver-related (10.7 vs. 20.0), lipid-related (12.0 vs. 14.7) or rash-related (8.7 vs. 13.3) adverse events were similar or lower for darunavir when compared to the control group. The majority of adverse events (92%) were grade 1 or 2 [2]. Grade 3 or 4 events were reported in 29% of each group and their profile was similar[12]. The most common were increased blood amylase (3%) and gamma glutamyltransferase (2%)[12]. Treatment discontinuations due to adverse events occurred in 4.3% of darunavir recipients in POWER 1,2 & 3[2], and 4.8% of control PI recipients in POWER 1 & 2[2,8].

PIs as a class are associated with a number of drug interactions, related to their inhibitory effects on CYP 3A4. Darunavir is no exception and a number of important interactions have been identified (see the Summary of Product Characteristics for further details).

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications:

In highly pre-treated HIV-1 infected adults, therapy has to be tailored based on a range of factors including their individual prior antiretroviral treatment histories and resistance profiles[5] (as was done for patients in the control groups of the POWER 1 & 2 studies). Some patients may have therapy options available and others may not. Commercially available PIs (to be boosted with ritonavir) include: amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir (see section 8.4).

Tipranavir is licensed for use in highly pre-treated patients with virus resistant to multiple PIs[6] and there are a range of other investigational agents that may be available on a compassionate-release basis[5].

7.2 Comparative effectiveness:

The POWER trials provide comparative data against a range of individualised control PI regimens. The most commonly used control PIs were lopinavir (36%), saquinavir (35%) and amprenavir/fosamprenavir (34%)[8]. NRTI use in the OBRs was consistent across all groups, the most commonly used being tenofovir (75%–95%), lamivudine (40%–65%) and didanosine (30%–45%)[11].

There are no direct comparative data for darunavir against tipranavir. The combined complete 48 week data from the two open-label RESIST studies indicate that more patients achieved and maintained a $\geq$ 1.0 $\log_{10}$ reduction in viral load below baseline in the tipranavir/ritonavir 500/200mg bd group than in the investigator-selected control PI group (33·6% vs. 15·3%; P<0·0001)[9]. Crudely, this compares with 61% vs. 15% (P<0.001) observed for darunavir/ritonavir 600/100mg bd vs. investigator-selected control PI group in the combined available 48-week data from POWER 1 & 2[2,7]. However, indirect comparative data should be interpreted with caution. Despite many similarities in the trial designs and methods, there are some important differences in the OBR regimens used, not all of which are addressed by group stratification. In the POWER trials, 23% of patients used double boosted PIs, 45% received enfuvirtide and

none received NNRTIs. In contrast, in the RESIST trials these figures were 0%, 25% and 17%[13].

Although not mentioned in the company submission, two phase III randomised, controlled, open-label trials to compare the efficacy, safety and tolerability of darunavir/ritonavir versus lopinavir/ritonavir in treatment-experienced (TMC114-C214) and treatment-naïve (TMC-C211) HIV-1 infected subjects are ongoing[14]. 48 week results of trial TMC114-C214 are expected to be reported July 2007[2].

Based on the limited data that are available, the safety and adverse event profile of darunavir seems to be consistent with other PI agents, but further safety data from on-going trials are required as a condition of its marketing authorisation[2].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider:

The key economic issues for AWMSG to consider are:

- whether the additional benefits offered by darunavir compared to current therapy justify the additional cost, and if so,
- whether the total budgetary impact of supporting the use of darunavir is acceptable

8.2 Review of published evidence on cost-effectiveness:

A US based cost effectiveness analysis of darunavir was presented at a recent conference[15]. This used the same model as that described in the company submission to AWMSG. However, the US analysis also incorporated data from tipranavir trials into the control PI arm, which has not been done for the NMG submission. The US analysis concluded that darunavir was cost-effective compared with the control PI arms (incremental cost per QALY US$4657). As this publication is only a poster presentation, this precludes a full review of this analysis. Standard searches conducted by WMP have not identified any other published economic studies of the use of darunavir.

8.3 Review of manufacturer's submission on cost-effectiveness:

The manufacturer's submission describes a Markov model that was used to assess the incremental cost per QALY of darunavir compared with control PI regimens in heavily pre treated HIV-1 patients.

A separate scenario analysis of darunavir/ritonavir vs. tipranavir/ritonavir has also been conducted using additional data from the RESIST studies of tipranavir[7]. Several assumptions are used in this scenario analysis that are not tested via sensitivity analyses.

The model 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. A lifelong time horizon was adopted and each Markov cycle was three months long[7].

Data from the POWER 1 and POWER 2 studies were used to provide the virological response to treatment and derive the probability of remaining in or moving between the relevant health states for darunavir and the control PI regimens. 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'[7]. The patient populations in these studies reflect the licensed indication for this agent and are likely to adequately represent the relevant patient population in Wales.

After the 'decline' stage, all patients are assumed to switch to a second regimen consisting of PIs and OBR, the response to which is assumed to be the same as the response to the control PI in the first regimen. Patients are assumed to remain on this second regimen for the remainder of their lives (except for enfuvirtide, which is assumed to be discontinued after a six month period in the CD4+ decline stage)[3]. Given that this population is already highly pre-treated and displays resistance to

multiple agents, the assumption that the second regimen will produce the same benefits as the previous control PI regimen is uncertain and has not been tested in the sensitivity analyses.

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[16]. Non HIV annual mortality rates were calculated from Welsh all cause mortality rates[17]. Utility values for the each health state of the model were obtained from a recent cost effectiveness analysis of lopinavir/ritonavir vs. nelfinavir[18], which used EQ5D derived utility values obtained from around 21,000 clinical trial participants. The model does not take account of any adverse events with darunavir or the control PI regimens. It is worth noting that the safety and adverse event profile of darunavir relative to other PIs has not yet been adequately characterised[2].

The model considers only direct health care resources and costs from the perspective of NHS Wales. No consideration is given to any personal and social service resources or costs, which is a limitation of the model as these could feasibly be substantial for (a proportion of) this patient group. Patterns of use in the POWER studies are used in the model, with the mean three monthly drug costs of each group being a weighted average of the costs of PIs, NRTIs and enfuvirtide[7].

Total non antiretroviral costs in the model consist of the costs of AIDS defining events and the costs of HIV related healthcare resource use. The annual probability of experiencing an AIDS defining event in each of the six CD4+ health states was estimated using data taken from a cohort of patients followed up via the EuroSIDA database[19]. This probability was applied to the estimated annual cost of treatment, which was then converted to three month costs. Three month HIV related healthcare resource use costs have been calculated using previous estimates of HIV related care, which date back as far as 1992–3[20]. There is, therefore, a degree of uncertainty with the assumed healthcare resource use data used in the model.

Costs and outcomes in the model were discounted at 3.5%, which is the preferred discount rate. One way and probabilistic sensitivity analyses, and best and worst case analyses have been conducted.

8.3.1 Summary of key findings from the manufacturer's submission on cost-effectiveness*:*

In the base case analysis, using a life time horizon, the incremental cost per QALY for darunavir over control PIs was estimated as £15,512. This is based on incremental drug costs of £23,670, a reduction in non drug costs of £2,204 and a gain of 1.384 QALYs.

In the one way sensitivity analyses of the effects of several parameters the incremental cost per QALY remained below £20,000. In the best and worst case analyses, the lowest and highest incremental costs per QALY were found to be £9,491 and £50,327. In the probabilistic sensitivity analysis, the probability of darunavir being cost effective at a willingness to pay threshold of £30,000 was predicted to be 93.5%.

In the scenario analysis, using a life time horizon, the incremental cost per QALY for darunavir over tipranavir was estimated as £12,233. This is based on incremental drug costs of £8,916, a reduction in non drug costs of £599 and a gain of 0.680 QALYs. The company submission states that the incremental drug costs of darunavir are a result of improved survival (0.678 years) and that the daily acquisition cost of ritonavir boosted

darunavir (£17.14) is less than ritonavir boosted tipranavir (£20.83). No sensitivity analysis has been presented.

8.4 Review of evidence on budget impact:

8.4.1 Summary of the evidence:

The manufacturer's submission includes a budget impact analysis that assessed the likely costs of darunavir over the next five years. The model is populated with historical and predicted data on the incidence and prevalence of HIV, estimates of the number of patients who meet the licensed indication for darunavir, and estimates of uptake. Only drug costs are included in the analysis[7]. The perspective adopted is that of NHS Wales. It is based on historical Welsh prevalence data, adapted where necessary by UK mortality rates. Regression analysis has been used to inflate historical figures to 2007.

Welsh data from the Health Protection Agency (HPA) from 2000 to 2005[21] has been used to construct a linear regression model to estimate the number of incident cases of HIV over the next five years. This model estimates that the number of incident cases will increase year on year by 15 cases. In 2007, the model predicts there will 155 incident cases of HIV-1 infection, rising to 216 in 2011[7].

Welsh data from the HPA[21] indicate that, between the point when diagnosis began in the 1980s and 2005, there have been 1,122 patients diagnosed with HIV-1. The UK HIV mortality rate of 20.8% (based on deaths in HIV patients since diagnosis began) has been applied to this figure to derive the number of live people in Wales in 2005 with HIV, which is estimated as 889. Applying the incidence figures above and a yearly death rate derived from HPA data (1.3%) the net number of HIV diagnosed patients in Wales is estimated to be 1,156 in 2007 rising to 1,846 in 2011[7]. This assumes that mortality rates remain constant over this period. The HPA source referenced in the company submission notes that subtracting reported deaths from the total of reported diagnosed HIV infected individuals cannot be regarded as providing a good estimate of the current prevalence of diagnosed HIV infection in the UK, due to the way the data are reported[21]. Moreover, the HPA provides prevalence data on the number of individuals with diagnosed HIV infection who attend for HIV related care within the NHS in Wales; with 760 patients reported for 2005[22].

A number of sources of data and assumptions have been used to calculate the anticipated use of darunavir. HPA data from 2004 indicates that 95.8% of diagnosed patients receive care[22]. Assuming the same rate applies in 2007, this amounts to 1,107 patients receiving care for HIV in Wales. Using data from a cohort study of UK patients (UK CHIC), 71.3% of patients had been treated with antiretroviral agents and 38.3% of these were estimated to be three class experienced in 2002[3]. Assuming these percentages are still the same, the company submission estimates that 302 patients in Wales are estimated to be three class experienced in Wales in 2007. Company data on file relating to a market research chart study involving 396 patient charts indicates that 70% of these patients have experience of two or more PIs (211 patients) and that 30% of patients will switch their PI for any reason in a given year (63 patients)[7].

These figures are not in line with data from the UK CHIC study, where 15.3% of patients (467 of 3,060) would be expected to have failed all three classes.[3]

Not all patients who require a switch will receive darunavir.

Additional information was provided here but remains commercial in confidence.

8.4.2 Summary of key findings from the manufacturer's submission on budget impact:

The direct costs of treatment used in the budget impact analysis consider only the drug costs of darunavir/ritonavir and alternative PI/ritonavir regimens. Agents used in OBRs are not included. The direct annual drug cost for darunavir/ritonavir is £6,256.10, based a daily cost of £14.89 for darunavir 300mg bd and £2.25 for ritonavir 100mg bd.

Additional information was provided here but remains commercial in confidence.

This assumes all drug costs remain the same. No discounting of costs is applied.

No direct savings of drug costs are identified, as darunavir is more expensive than the comparator PIs. Tipranavir is not included in these incremental cost calculations. No sub-group analysis has been conducted.

See Appendix 2 for further details on the economic evidence and budget impact analysis presented in the company submission.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- The British HIV Association (BHIVA) issued updated guidelines[5] on antiretroviral treatment of HIV-1 in adults in 2006. Although darunavir is mentioned in these guidelines, they were issued before the drug was licensed and little information specific to this drug is contained. However, the general principles of the management of treatment experienced patients are discussed.
- The London New Drugs Group, on behalf of the HIV Drugs and Treatment sub group of the London HIV Consortium, issued guidance on the use of darunavir before it had received a marketing authorisation[13]. This recommended that the choice to use darunavir as opposed to tipranavir should be based on the mutations of the patient's virus, drug toxicities and drug interactions. Use, patient outcome and cost data for darunavir will be monitored as part of the Trusts (within London) data and audit returns to the London HIV Consortium.
- The BHIVA guidelines recommend that if antiretroviral therapy is started in the context of primary HIV infection, it should normally only be in the setting of a clinical trial[5]. Clinical trials of existing and investigational agents are very common in HIV-1, so many newly diagnosed and treatment experienced patients will be being closely monitored for their treatments and outcomes as a normal part of their care.
- The Health Protection Agency, in collaboration with National Public Health Survey for Wales, conduct an annual survey (SOPHID) of all patients seen for HIV related treatment or care[23].
- As darunavir is intended for patients who are highly pre treated and may have few therapeutic options available to them, it will be initiated by specialists and therefore would not be currently deemed suitable for shared care.

9.2 Previous AWMSG/NICE advice:

- Tipranavir (Aptivus®) – pending appraisal in August 2007
- Emtricitabine (Emtriva®) – pending appraisal in June 2007
- Emtricitabine/tenofovir DF (Truvada®) – pending appraisal in June 2007
- Enfuvirtide (Fusion®) –accepted for use (supported with restrictions, May 2004)[24]

9.3 Other points:

- The EPAR for darunavir notes that there is a need to further characterise its safety profile. The positive opinion of darunavir granted by the Committee for Medicinal Human Products is conditional upon further demonstration of safety[2].
- A proportion of patients may already be receiving darunavir due to its prior availability via compassionate use arrangements.
- A phase III trial is investigating darunavir in treatment naïve patients.

9.4 Medical Expert:

Medical expert opinion was sought and provided prior to the meeting.

9.5 Patient Interest Group:

A patient interest group submission by the Terrence Higgins Trust was provided.

References:

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Appendix 1. Additional Clinical Information

Nothing additional to add.

Appendix 2. Health Economic Review

Company submission - economic evidence

1. Description of manufacturer's submission

The manufacturer's submission describes a Markov model that was used to assess the incremental cost per QALY of darunavir compared with control PI regimens in heavily pre-treated HIV-1 patients. The model 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])[7].

The model has previously been used to estimate the cost utility of darunavir in a US healthcare system[14]. As data beyond 48 weeks were not available, the expert opinion of seven UK based HIV specialists were sought on issues of duration of immunological response based on virological responses and the initiation of treatment regimens. However, the company submission does not state whether the overall model structure has been externally tested or validated.

In addition to the sensitivity analyses that were conducted, the company submission also describes a scenario analysis, in which tipranavir is modelled as the comparator[7].

2. Population

The model was designed to assess the cost utility of ritonavir-boosted darunavir, in combination with other antiretroviral agents, in highly pre-treated HIV-1 infected adults[7]. This reflects the licensed indication for darunavir[1].

Data from the POWER 1 and POWER 2 studies were used to provide the virological response to treatment and derive the probability of remaining in or moving between the relevant health states for darunavir and the control PI regimens. The patient populations in these studies are likely to adequately represent the relevant patient population in Wales.

Additional data for the scenario analysis of darunavir against tipranavir were derived from the RESIST trials[9]. These assessed tipranavir/ritonavir in a similar patient population who were also highly pre treated.

3. Perspective and time horizon

The model considers only direct costs from the perspective of NHS Wales[7]. No consideration is given to any personal and social service costs/resources, which is a limitation of the model as these could feasibly be substantial for a proportion of this patient group.

As HIV infection is life long, the time horizon chosen for the analysis was stated to be life-long. Although this is a reasonable assumption, no further information is provided in this respect (except in sensitivity analysis).

Each Markov cycle was set at three months, which the company submission highlights is in line with other Markov models of HIV[7]. It should be noted that the efficacy analyses in the POWER studies were conducted at 24 weeks (for the primary endpoint)

and 48 weeks. The model assumes that the CD4+ change from baseline for each level of virological response occurs linearly over the first 24 weeks and applies this rate to the three month cycle. This assumption is not further explored. 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).

4. Comparator

The control PI groups used in the POWER studies (and in the RESIST studies of tipranavir) are appropriate comparators for use in the model. They reflect current clinical practice recommendations for the treatment of highly pre treated patients[2]. However, the company submission appears to suggest that the proportion of patients receiving each of the various NRTIs in their OBR was exactly the same in the darunavir and the control PI groups[7]. Although there was consistency in the use of NRTIs across the groups, the proportions receiving each of the different NRTIs differed[11]. In addition, for the scenario analysis, it should be noted that there were some differences in the other antiretroviral treatments received as part of the OBRs, which do not appear to have been addressed in the model. In the POWER trials, 23% of patients used double boosted PIs and none received NNRTIs. In contrast, in the RESIST trials these figures were 0% and 17%[13]. Enfuvirtide use also differed between the POWER and RESIST trials (45% vs. 25%, respectively)[13], but the scenario analysis assumes that its use was the same[7].

5. Clinical inputs

5.1 Clinical effectiveness

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 POWER trials[7]. As efficacy analyses were conducted at 24 and 48 weeks, the various parameters of the model are assumed to take place in a linear fashion or are made to fit around these time points. However, it should be noted that these are artificial time points. 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'.

5.1.1 Transition probabilities and stages of CD4+ count changes

The 24 week data from the POWER studies were used to estimate the percentage of patients falling into the virological response categories of undetectable, partial suppression and no suppression. The model assumes that the change in CD4+ count from baseline for each level of virological response occurs linearly over the first 24 weeks. Graphical data on the combined mean change from baseline in CD4+ count over 48 weeks for all levels of virological response in the darunavir group does not appear to support this assumption, instead indicating a very rapid increase up to week 4, a more steady increase up to week 16 and then a plateau to week 24[25]. Sensitivity analysis has been conducted around the rate of change of CD4+ counts, but is limited to the boundaries of the 95%CI around this assumed rate. The mean increases and standard deviations in CD4+ cell count in the first 24 weeks were used to construct a normal distribution with which the transition probabilities for the different virological response categories for the CD4+ 'initial increase' stage were estimated.

The CD4+ cell count data between weeks 24 and 48 were used to estimate the mean CD4+ cell count changes in each cycle for the 'stable/slow increase' stage. Transition probabilities were derived as for the 'initial increase' stage by assuming that patients

are uniformly distributed within each CD4+ health state and that all achieve the mean CD4+ cell count increase.

For the CD4+ 'decline' stage, 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)[26], 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)[27]. By inputting the baseline viral load from patients in the POWER 1 and 2 studies 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 three classes of antiretrovirals but who remain on therapy (as in the PLATO 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[7].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 using twice the rate of decline has been conducted.

The duration of the CD4+ 'initial increase' stage was taken from the POWER trials. The duration of this period is assumed to be six months for all virological responses except the control PI virological response category 'undetectable'. The CD4+ count increase observed in this group is stated to be more gradual and sustained over the 48 week period, and so the duration of the initial increase stage has been assumed to be one year for this category. One way sensitivity analysis on the duration of the 'initial increase' stage does not appear to have been conducted, but this is included in the probabilistic sensitivity analysis.

As data beyond 48 weeks was not available, expert opinion was sought for the duration of the 'stable/slow increase' and the 'decline' stages[7]. For the virological response category of 'no suppression' the duration of the 'stable/slow increase' CD4+ stage is assumed to be zero months. The model also assumes that the overall time to treatment failure (i.e. time to the start of the 'decline' CD4+ stage) is the same for the control PI and the darunavir 'undetectable' virological response groups. This means that the duration of the 'stable/slow increase' CD4+ stage for the control PI group is shorter than the darunavir PI group. No justification is provided for this assumption in the model and it does no appear to have been tested in any sensitivity analyses. The duration of the 'decline' CD4+ stage in all groups (time to the start of the second treatment regimen), irrespective of virological response, has been assumed as six months, based on expert opinion[7].

5.1.2 Treatment regimens

After the 'decline' stage, all patients are assumed to switch to a second regimen consisting of PIs and OBR, the response to which is assumed to be the same as the response to the control PI in the first regimen. Patients are assumed to remain on this second regimen for the remainder of their lives (except for enfuvirtide, which is assumed to be discontinued after a six month period in the CD4+ decline stage)[7]. Given that this population is already highly pre treated and displays resistance to multiple agents, the assumption that the second regimen will produce the same benefits as the previous control PI regimen is uncertain and has not been tested in the

sensitivity analyses. The use of enfuvirtide was a significant predictor of response to PIs[2,5] and this agent was used in only around 46% and 42% of the darunavir and control PI groups in the POWER studies, respectively. In addition, tipranavir was not allowed as a control PI in the POWER studies, and the BHIVA guidelines note that, in those patients developing resistance to darunavir, the majority of isolates that were sensitive to tipranavir at baseline remained sensitive to tipranavir[5]. It should also be considered that a proportion of this patient population that fails the first modelled treatment regimen will have exhausted their treatment options, and the BHIVA guidelines note that, in some of these patients, it may be better to wait to change treatment until an investigational treatment becomes available[5].

5.2 Health outcomes

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[16], transformed where necessary to match the health states of the model defined by CD4+ cell count, and converted to provide three month probabilities of death[7]. Non HIV annual mortality rates were calculated from Welsh all cause mortality rates[17] by subtracting the HIV related mortality rates calculated as described above. Three age ranges are considered in the model (20–39 years, 40–64 years and 65-plus) and weighted average non HIV death rates were calculated for these, transformed into three month rates[7].

Utility values for the each health state of the model were obtained from a recent cost effectiveness analysis of lopinavir/ritonavir vs. nelfinavir as a first line antiretroviral regimen[18]. 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 using a range of utility values obtained from other sources.

5.3 Adverse events

The model does not take account of any adverse events with darunavir or the control PI regimens. The safety and adverse event profile of darunavir relative to other PIs has yet to be characterised[2].

6. Healthcare resource utilisation and cost

The model considers only direct health care resources and costs from the perspective of NHS Wales[7]. No consideration is given to any personal and social service resources or costs, which is a limitation of the model as these could feasibly be substantial for (a proportion of) this patient group. Resource use and costs of adverse events with darunavir or control PIs have not been specifically incorporated in the model.

All antiretroviral drug costs are presented in 2006 UK£. Patterns of use in the POWER studies are used in the model, with the mean three monthly drug costs of each group being a weighted average of the costs of PIs, NRTIs and enfuvirtide[7].

Non drug costs are presented in 2005 UK£, which creates a slight discrepancy. Total non antiretroviral costs in the model consist of the costs of AIDS defining events and the costs of HIV related healthcare resource use. The cost of AIDS defining events has been obtained from a previous estimate based on 2001 costs and inflated to 2005 costs using PSSRU Unit Costs for Health and Social Care. The annual probability of

experiencing an AIDS defining event in each of the six CD4+ health states was estimated using data taken from a cohort of patients followed up via the EuroSIDA database[19]. This probability was applied to the estimated annual cost of treatment, which was then converted to three month costs. Three-month HIV related healthcare resource use costs have been calculated using previous estimates of HIV related care, which date back as far as 1992–3[20]. Although the costs of this care have been inflated to 2005 prices, it is likely that the patterns of healthcare resource use today would be significantly different from those in 1992–3. There is, therefore, a degree of uncertainty with the assumed healthcare resource use data used in the model. Sensitivity analysis on these costs has been conducted.

7. Discounting

Costs and outcomes in the model were discounted at 3.5%, which is the preferred discount rate. Sensitivity analyses were conducted to explore the effect of different discount rates (0% and 6%) on the model outputs[7].

8. Results[7]

8.1 Base-case analysis — Darunavir vs. control PIs used in the POWER 1 & 2 studies

Using a life-time horizon, the incremental cost per QALY for duranavir over control PIs was estimated as £15,512. This is based on incremental drug costs of £23,670, a reduction in non drug costs of £2,204 and a gain of 1.384 QALYs. No confidence intervals have been provided for this or any other incremental cost per QALY estimate.

8.2 Scenario analysis — Darunavir vs. tipranavir

The scenario analysis uses a number of untested assumptions to model darunavir against tipranavir. These include the assumption that the non PI component of the tipranavir arm is the same as the OBR used in the darunavir arm of the POWER trials, that enfuvirtide use is the same for in each arm and that the mean CD4+ counts for the different categories of virological response are in the same ratio as in the darunavir arm. It is unclear how these assumptions may influence the outputs of the model.

Using a life time horizon, the incremental cost per QALY for duranavir over tipranavir was estimated as £12,233. This is based on incremental drug costs of £8,916, a reduction in non drug costs of £599 and a gain of 0.680 QALYs. The company submission states that the incremental drug costs of darunavir are a result of improved survival (0.678 years) and that the daily acquisition cost of ritonavir-boosted darunavir (£17.14) is less than ritonavir-boosted tipranavir (£20.83). No sensitivity analysis has been presented.

9. Sensitivity analysis[7]

9.1 One way sensitivity analyses

The manufacturer's submission presents the results of series of one way sensitivity analyses around: mortality rates (upper and lower 95%CI, alternative sources), three monthly risk of AIDS defining events (±25%), three monthly non drug costs (±25%), utility values (alternative sources), discount rates (0%, 6%), comparator PIs (indinavir, lopinavir [no references supplied]), time to discontinuation of enfuvirtide (from 0 months to no discontinuation), CD4+ cell counts in 'initial increase' (upper and lower 95%CI), CD4+ cell counts in 'stable/slow increase' (alternative sources, no increase to 100cells/year), CD4+ cell counts in 'decline' (base case rate x 2), duration of CD4+

'stable/slow increase' (1.5 to 7 years), duration of decline in CD4+ before switch to second regimen (0 to 5 years), and time horizon (5 years and 10 years).

Results are presented as a Tornado diagram, which indicates that the incremental cost per QALY remained below £20,000 across the range of values tested. The parameter producing the largest change in incremental cost per QALY was the time horizon, which led to a decrease when set to 10 or 5 years. The largest increase in incremental cost per QALY was related to changes in utility values.

9.2 Best case and worst case analyses

The company submission states that each parameter was set to the value that resulted in the highest and lowest cost effectiveness ratios, generating incremental costs per QALY of £9,491 and £50,327. It is not clear whether the parameters tested were the same as those in the one way sensitivity analyses or not.

9.3 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed on the base case scenario using 1,000 simulations. The parameters considered were: population at model entry (age, gender and CD4+ distribution), virological response (number of patients in each virological response category in the POWER and RESIST trials), immunological response (mean change in CD4+ counts during 'initial increase, 'stable/slow increase', and 'decline' stages; duration of first two stages), clinical outcomes data (mortality rates, utility values and opportunistic infection rates), the costs of control PIs (varied by assuming all patients receive the cheapest PIs, or patients receive the most expensive PIs), and other HIV costs (varied by 25%).

At a willingness to pay threshold of £30,000 per QALY, the probability of cost-effectiveness is predicted to be 93.5%. At a threshold of £20,000 the probability is 71.5% and at £40,000 is 96.6%.

Manufacturer's submission - budget impact analysis

1. Description of manufacturer's submission

The manufacturer's submission includes a budget impact analysis that assessed the likely costs of darunavir over the next five years. The model is populated with historical and predicted data on the incidence and prevalence of HIV, estimates of the number of patients who meet the licensed indication for darunavir, and estimates of uptake. Only drug costs are included in the analysis[7].

2. Perspective and time horizon

The perspective adopted by the budget impact analysis is that of NHS Wales. It is based on historical Welsh prevalence data, adapted where necessary by UK mortality rates. Regression analysis has been used to inflate historical figures to 2007. A five year time horizon is used[7].

3. Incident cases

Welsh data from the Health Protection Agency (HPA) from 2000 to 2005[21] has been used to construct a linear regression model to estimate the number of incident cases of HIV over the next five years. This model estimates that the number of incident cases will increase year on year by 15 cases. In 2007, the model predicts there will 155 incident cases of HIV-1 infection, rising to 216 in 2011[7].

4. Prevalent cases

Welsh data from the HPA[21] indicate that, between the point when diagnosis began in the 1980s and 2005, there have been 1,122 patients diagnosed. The UK mortality rate of 20.8% (since diagnosis began) has been applied to this figure to derive the number of live people in Wales in 2005 with HIV. This derives a figure 889. Applying the incidence figures above and a yearly death rate derived from HPA data (1.3%) the net number of cases is estimated to be 1,156 in 2007 rising to 1,846 in 2011[7]. This assumes that mortality rates remain constant over this period. The HPA source referenced in the company submission notes that subtracting reported deaths from the total of reported diagnosed HIV infected individuals cannot, be regarded as providing a good estimate of the current prevalence of diagnosed HIV infection in the UK, due to the way the data are reported[21]. However, in the absence of other estimates, this is likely to be the best available method.

5. Anticipated use of darunavir

A number of sources of data and assumptions have been used to calculate the anticipated use of darunavir. HPA data from 2004 indicates that 95.8% of diagnosed patients receive care[22]. Assuming the same rate applies in 2007, this amounts to 1,107 patients receiving care for HIV in Wales. Using data from a cohort study of UK patients (UK CHIC), 71.3% of patients had been treated with antiretroviral agents and 38.3% of these were estimated to be three-class experienced in 2002[3]. Assuming these percentages are still the same, the company submission estimates that 302 patients in Wales are estimated to be three class experienced in Wales in 2007. Company data on file relating to a market research chart study (involving 396 patient charts) carried out with 50 UK clinicians who treat HIV patients indicates that 70% of these patients have experience of two or more PIs (211 patients) and that 30% of patients will switch their PI for any reason in a given years (63 patients)[7].

Not all patients who require a switch will receive darunavir.

Additional information was provided here but remains commercial in confidence.

6. Results[7]

6.1. Base-case

The direct costs of treatment used in the budget impact analysis consider only the drug costs of darunavir/ritonavir and alternative PI/ritonavir regimens. Agents used in OBRs are not included. The direct annual drug cost for darunavir/ritonavir is £6,256.10, based a daily cost of £14.89 for darunavir 300mg bd and £2.25 for ritonavir 100mg bd. The cost of alternative PI regimens are listed below:

PI regimens	Cost per year
Tipranavir/ritonavir 500/200mg bd	£7604.17
Amprenavir/ritonavir 600/100mg bd	£3367.13
Fosamprenavir/ritonavir 700/100mg bd	£4166.11
Atazanavir/ritonavir 300/100mg od	£4662.15
Indinavir 800mg tds	£2753.07
Lopinavir/ritonavir 400/100mg bd	£3739.91
Nelfinavir 1250mg bd	£3323.45
Saquinavir/ritonavir 1000/100mg bd	£4066.51
Source: BNF No. 53, 2007[28]	

Additional information was provided here but remains commercial in confidence.

This assumes all drug costs remain the same. No discounting of costs is applied.

No direct savings of drug costs are identified, as darunavir is more expensive than the comparator PIs. Tipranavir is not included in these calculations.

6.2. Sub-group analysis

No sub-group analysis has been conducted.

7. Sensitivity analysis[7]

No sensitivity analyses have been conducted around any of the assumptions.