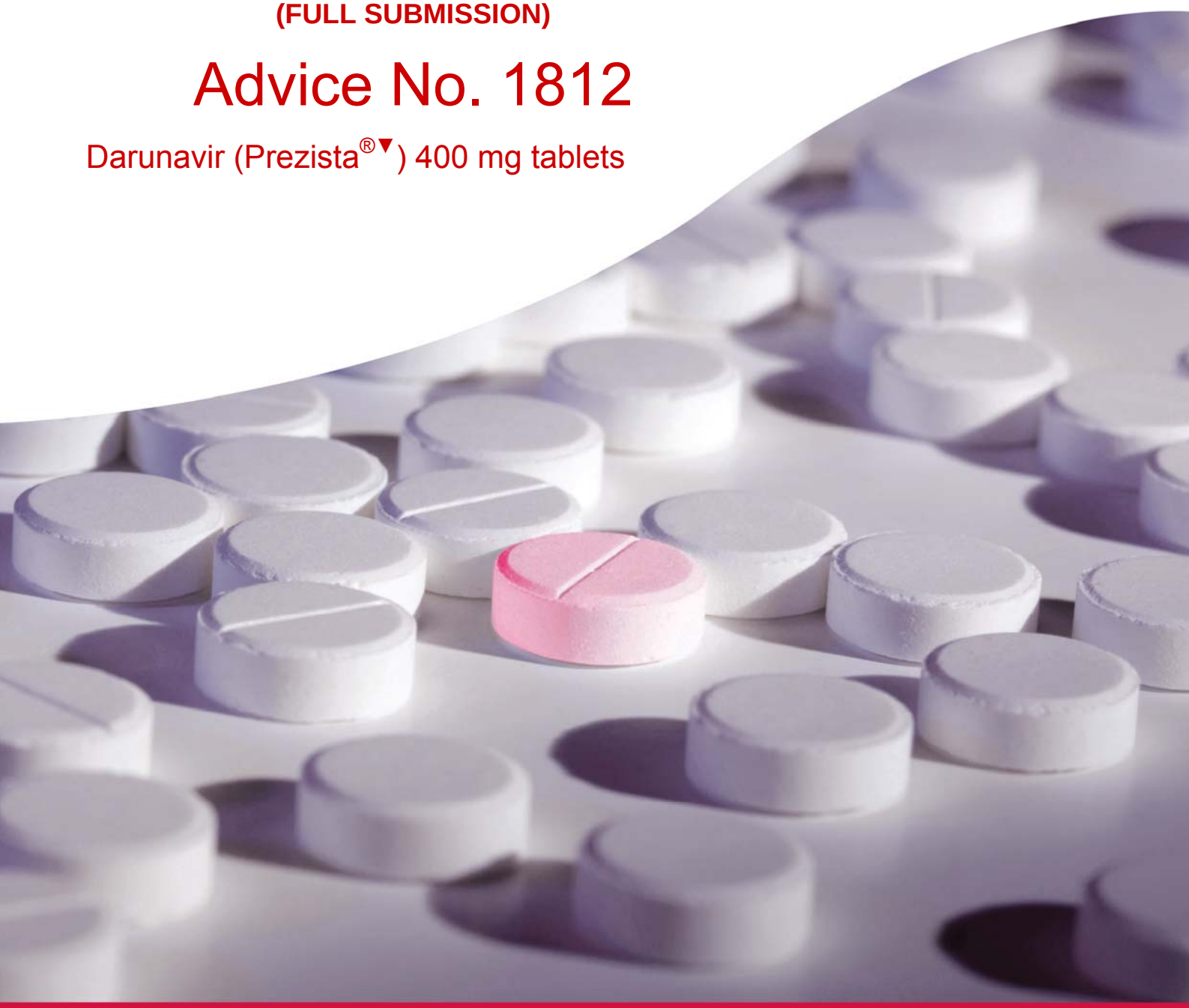
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 1812

Darunavir (Prezista®▼) 400 mg tablets



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 1812
Darunavir (Prezista®▼) 400 mg tablets

This assessment report is based on evidence submitted by Janssen-Cilag Ltd on 2 February 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration[2]	Darunavir (Prezista®▼) 800 mg once-daily (od, administered as two 400 mg tablets), co-administered with low dose ritonavir (100 mg od) is licensed for the treatment of HIV-1 infection in antiretroviral therapy (ART)-experienced adults with no darunavir resistance-associated mutations, and who have plasma HIV-1 RNA < 100,000 copies/mL and a $CD4^+$ cell count ≥ 100 cells/mm^3.
Dosing[2]	Darunavir 800 mg once-daily may only be used in the patient population specified above. In all other ART-experienced adults, or if HIV-1 genotype testing is not available, the recommended dose of darunavir is 600 mg twice-daily taken with ritonavir 100 mg twice-daily. Darunavir must be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics (SPC) for ritonavir must therefore be consulted prior to initiation of darunavir therapy. Darunavir should be taken within 30 minutes of completion of a meal. Darunavir therapy should be initiated by a physician experienced in the management of HIV infection.
Marketing authorisation date[2]	Date of original marketing authorisation: 12 February 2007. Date of extension to marketing authorisation: 7 March 2011.

2.0 DECISION CONTEXT

2.1 Background

Human immunodefiency virus (HIV) is a lentivirus, of which two forms (HIV-1 and HIV-2) are currently known. HIV-1 is the more virulent and is responsible for the current pandemic. The virus infects immune system cells leading to depletion of $CD4^+$ T cells and loss of cell-mediated immunity. If left untreated, this chronic disease state ultimately results in immune failure and death from overwhelming infections or malignancies. This state is known as acquired immunodeficiency syndrome, or AIDS[3].

While there is no cure for HIV, the various enzymes in the viral life cycle are useful targets for arresting its spread, and thus reducing the morbidity and mortality of HIV-infected patients. Several medicines from different classes (targeting different HIV enzymes) are combined to create highly active antiretroviral therapies (HAART). Nucleoside-analogue and non-nucleoside reverse transcriptase inhibitors (NRTI and NNRTI respectively) hamper the formation of the DNA transcript. Protease inhibitors (PI) interfere with the cleavage of synthesised polypeptides into active viral proteins that are essential for the HIV replication cycle, thus reducing infectivity. Newer entry inhibitors reduce the ability of the virus to infiltrate cells[3].

One of the challenges in treating HIV infections is the genetic lability of the virus. The reverse transcription process is error prone and mutations arise at a rapid rate, some of which result in resistance to established therapies. Darunavir is a protease inhibitor that appears to work well against infection in patients with wild-type HIV or one of many mutant forms, although some darunavir resistance associated mutations (RAMs) have been identified. Darunavir was originally licensed for use in treatment-experienced patients as a 600 mg darunavir/100 mg ritonavir twice-daily (bid) dose. This report reviews the data in support of using a once-daily 800 mg/100 mg dosing regimen[3].

The company estimates there to be 1,575 HIV-positive patients in Wales[1], 619 of whom are treatment-experienced patients who could potentially receive this once-daily dose of darunavir, although the anticipated numbers of patients treated annually are estimated by the company to be 224 in 2012, rising to 391 in 2015 (refer to Section 5 for further information)[1].

2.2 Comparators

The comparators requested by the Welsh Medicines Partnership* were atazanavir (Reyataz®▼) and lopinavir (Kaletra®). The company suggest that lopinavir is not widely used in the UK, and its use is declining for the indication under consideration. The company therefore view atazanavir as the most appropriate comparator to darunavir. Clinical and pharmacoeconomic evaluation of darunavir against both atazanavir and lopinavir has been included, but the main focus of the company submission is the comparative effectiveness of darunavir and atazanavir (refer to Section 4 for further information).

2.3 Guidance and related advice

- British HIV Association (BHIVA) guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy (2008)[4].
- European AIDS Clinical Society. European guidelines for the clinical management and treatment of HIV-infected adults in Europe (2011)[5]

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of darunavir:

- 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, and where resistance profiling suggests it is appropriate[6].
- 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.[7]

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The data in support of the clinical effectiveness of once-daily darunavir derives from an assessment of once-daily darunavir versus boosted atazanavir and lopinavir in the form of a mixed treatment comparison (MTC), and a trial directly comparing once-daily and twice-daily darunavir treatment regimens. The major trials (including dosing regimens) that are included in the mixed treatment comparison are detailed in Table A1, Appendix 1, with key aspects discussed below.

* In April 2012 the Welsh Medicines Partnership became a part of the All Wales Therapeutics and Toxicology Centre (AWTTC).

3.1 Comparison of darunavir treatment regimens (ODIN)[1,8]

The ODIN (Once-daily Darunavir In treatment-experieNced patients) trial[8] is a randomised open-label phase III trial comparing the efficacy and safety of 800 mg darunavir boosted with 100 mg ritonavir (800/100 mg) taken once-daily (n = 294) with that of the 600 mg darunavir boosted with 100 mg ritonavir (600/100 mg) combination taken twice-daily (n = 296). In both cases the patients also received other HIV medicines as part of an optimised background regimen (OBR).

The primary objective was the demonstration of non-inferiority of the 800/100 mg once-daily regimen compared with the 600/100 mg twice-daily regimen, in terms of confirmed virologic response (HIV-1 RNA < 50 RNA copies/mL) at week 48. For the intent-to-treat (ITT) population, 72.1% of the 800/100 mg subjects had viral loads below 50 RNA copies/mL at week 48 compared to 70.9% of the 600/100 mg subjects. The difference in response rates between treatment groups was 1.2% (95% confidence interval -6.1%, 8.5%); a predefined non-inferiority margin of 12% was specified and therefore non-inferiority was demonstrated. In the once-daily group, virologic failure was noted in 22.1% of patients (18.2% in the twice-daily treated group). $CD4^+$ count, a secondary endpoint, increased in both treatments by week 48 (+100 and +94 cells/mm^3 respectively). Health-related quality of life (HRQoL) was assessed using the Functional Assessment and HIV infection (FAHI) score. Both groups reported improvements during treatment of 2.7 points (800/100 mg) and 3.1 points (600/100 mg) by week 48. The difference was not statistically significant. A total of 13.9% of patients in the once-daily group discontinued early, compared with 16.2% in the twice-daily group.

As the ODIN trial contained subjects (n = 126) outside the licensed indication under consideration (HIV RNA > 100,000 copies/mL; $CD4^+$ count < 100 cells/mm^3), the company submission included an analysis of the licence-compliant subgroup (commercial in confidence data removed)

3.2 Mixed treatment comparison[1,9]

Based on the results of a systematic literature review, a mixed treatment comparison was conducted with the aim of assessing the comparative efficacy, safety and tolerability of darunavir with atazanavir and lopinavir in treatment-experienced HIV patients[1,10]. The only trials identified that directly compare one PI with another are POWER 1 and 2[11,12], TITAN[12,13] and BMS-045[12,14]. These studies are summarised in Table A1, Appendix 1. Several other studies were included in the mixed treatment comparison: DE-ESCALATE[15] was concerned only with atazanavir, while Podzamczer et al (2007)[16], Benson et al (2002)[17], M06-082[18], M98-957[19] and M98-888[20] are trials involving lopinavir. These trials will therefore not be discussed further.

While the inclusion and exclusion criteria for the different trials were largely consistent, there were aspects of heterogeneity between trials, particularly in the level of treatment experience of study subjects (see Appendix 1 for details), a limitation that is acknowledged by the company[1]. Several aspects of efficacy are considered in the comparison, including virological failure, new PI and NRTI mutations, in addition to suppression of HIV RNA to < 50 and < 400 RNA copies/mL. The absolute efficacy data for these are summarised in Table 1, with Table 2 providing estimates of the relative changes in $CD4^+$ cell counts from baseline at 48 weeks.

Table 1. Summary of absolute efficacy data from mixed treatment comparison[9]

Treatment	Absolute efficacy, % [95% credibility intervals]				
	Virological failure	New PI mutations	New NRTI mutations	HIV RNA < 50 copies/mL at week 48	HIV RNA < 400 copies/mL at week 48
D/R 600/800 mg bid	13.9 [0.9,56.3]	3.1 [0.1,17.8]	2.4 [0.1,14.2]	61.9 [12.1,96.1]	68.1 [17.3,96.9]
D/R 800/100 mg od	19.1 [0.4,83.0]	24.3 [0.1,98.9]	5.7 [10.0,45.2]	61.6 [4.7,98.7]	
L/R 400/100 mg bid	21.6 [17.2,26.4]	5.5 [3.8,7.4]	5.0 [2.8,7.7]	53.3 [48.2,58.4]	61.4 [55.9,66.8]
L/R 400/200 mg bid				63.0 [12.3,96.6]	65.4 [13.1,97.0]
L/R 533/133 mg bd					69.8 [16.9,97.7]
L/R 800/200 mg od		5.0 [0.2,27.4]		55.5 [9.4,95.5]	
A/S 400/1200 mg od				34.8 [3.4,85.7]	43.1 [4.9,90.4]
A/R 300/100 mg od				45.9 [5.8,91.6]	57.8 [10.0,95.1]
PI/R				30.0 [0.78,92.1]	39.4 [4.3,88.5]
D: darunavir; L: lopinavir; A: atazanavir; R: ritonavir; S: saquinavir; PI: protease inhibitor control group.					

Table 2. Estimates, derived from a mixed treatment comparison, of relative change in CD4$^+$ cell count from baseline to 48 weeks[9]

Treatment, (cells/mm^3) ([95% credibility limit])	D/R 800/100 mg od	L/R 400/100 mg bid	A/R 300/100 mg od
D/R 800/100 mg od	n/a	-15 [-47,+17]	-7 [-72,+55]
L/R 400/100 mg bid	+15 [-17,+47]	n/a	+8 [-63,+51]
A/R 300/100 mg od	+7 [-55,+72]	-8 [-63,+51]	n/a
D: darunavir; L: lopinavir; A: atazanavir; R: ritonavir.			

As acknowledged by the company, the limited evidence available to compare different treatments means that for many of the outcomes, the credible intervals for the efficacy estimates are large, indicating considerable uncertainty. Discussion of the results in the company submission highlights the relative performance of the treatments. However, these are invariably based on point estimates with no statistically significant differences between the groups. Overall, the efficacy data suggest that once-daily darunavir boosted with ritonavir (800/100 mg) is non-inferior to the other treatments assessed in this comparison.

3.3 Comparative safety

The safety data from the MTC[9] considered increases in liver enzymes, cholesterol, triglycerides, nausea and diarrhoea at 48 weeks, and the incidence of any grade 3–4 adverse event or any serious adverse event at 48 weeks. There was no significant difference in the overall incidence of grade 3–4 adverse events or serious adverse events between darunavir 800/100 mg once-daily and the comparators. With regards to alanine transaminase (ALT) there were more grade 2–4 elevations with lopinavir/ritonavir and darunavir/ritonavir (600/100 mg) than with darunavir/ritonavir (800/100 mg). The incidence of grade 3–4 elevations was comparable for all treatments. Results of the MTC suggested hypercholesterolaemia or hypertriglyceridaemia were less frequent with darunavir/ritonavir 800/100 mg once-daily than 600/100 mg twice-daily. However, it should be noted that none of the differences discussed were statistically significant.

In the ODIN trial the safety profiles were broadly similar between treatment arms[8,12] with 77.0% of 600/100 mg twice-daily treated patients experiencing at least one adverse event, compared to 76.2% in the 800/100 mg once-daily group. Compared with the 600/100 mg treatment arm, fewer patients in the 800/100 mg arm developed hypertriglyceridaemia (5.2% versus 11.0%) or hypercholesterolaemia (10.1% versus 20.6%). For the POWER 1, POWER 2 and Titan trials[12] the differences seen in the safety profiles were small and the safety signals comparable across treatment arms.

3.4 AWTTC critique

- In the absence of any clinical evidence directly comparing the effectiveness of darunavir with the comparators (atazanavir and lopinavir), the company have carried out a mixed treatment comparison of these therapies The data presented for the mixed treatment comparison were derived from several trials that were heterogeneous in terms of study populations and dosing frequencies. All trials included treatment-experienced patients, but the level of previous treatment experience varies between trials. The results suggest that there is no statistically significant difference in any relevant efficacy or safety outcome between darunavir, atazanavir and lopinavir.
- Although twice-daily darunavir is not considered to be a comparator to once-daily darunavir for the purposes of this assessment, results of the ODIN trial are included as they provide direct and robust evidence for the non-inferiority of once-daily darunavir in relation to the twice-daily dosing regimen. The non-inferiority conclusion strictly applies only to the whole study population, as the subset of patients that meets the licensed indication does not provide the statistical power to demonstrate this. However, the results for the subgroup analysis are in line with the ITT group.
- Once-daily darunavir has a reduced pill burden compared to the existing twice-daily regimen. There is evidence that adherence is greater with once-daily HAART regimens, with a corresponding improvement in the effectiveness of treatment[4,21–26]. However, this advantage does not apply to patients switching from an existing once-daily regimen (i.e. atazanavir or lopinavir), where it is assumed there will be little difference in adherence.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost-utility analysis of darunavir 800 mg co-administered with ritonavir 100 mg once-daily for the treatment of HIV-1 infection in antiretroviral therapy-experienced adults with no darunavir RAMs and who have plasma HIV-1 RNA < 100,000 RNA copies/mL and $CD4^+$ cell count ≥ 100 cells/mm³. In the base case analysis, the comparator is atazanavir 300 mg co-administered with ritonavir 100 mg once-daily, with lopinavir 400 mg co-administered with ritonavir 100 mg twice-daily considered in a scenario analysis.

The analysis is based on an adaptation of a previous Markov model submitted to AWMSG by the company as part of a previous appraisal of darunavir. Patients enter the model in one of six $CD4^+$ cell count states based on baseline characteristics of patients in the ODIN trial of once-daily versus twice-daily darunavir/ritonavir. Transition probabilities among possible $CD4^+$ cell-count states are estimated according to patients' virologic responses at 24 weeks derived from the ODIN trial. In the absence of direct comparative data, the company has conducted indirect mixed treatment

comparisons to provide relative effectiveness data for the comparators (see Section 3.2). Following failure of darunavir or the comparators, patients may receive a further two lines of antiretroviral therapy, determined from expert opinion. The model assumes a three-month cycle and a lifetime analytical time horizon. See Appendix 2 for further details.

4.1.2 Results

Results of the base case analysis of darunavir/ritonavir 800/100 mg once-daily compared to atazanavir/ritonavir 300/100 mg once-daily are summarised in Table 3. The darunavir treatment strategy is estimated to be marginally less costly and more effective compared to atazanavir treatment.

Table 3: Company-reported results of the base case analysis of darunavir/ritonavir 800/100mg once-daily compared to atazanavir/ritonavir 300/100 mg once-daily in the treatment of HIV-1 infection in antiretroviral therapy-experienced adults

	Darunavir/ritonavir	Atazanavir/ritonavir	Difference
Antiretroviral drug costs	£217,508	£217,725	-£218
Other drug costs	£28,045	£28,772	-£728
Inpatient care	£6,052	£6,161	-£109
Outpatient care	£6,526	£6,494	£32
Total cost	£258,130	£259,153	-£1,023
Total life years	15.234	15.083	0.150
Total QALYs	14.111	13.951	0.160
Incremental cost per QALY gained	**Darunavir strategy dominates***		
***Darunavir/ritonavir is both less costly and more effective than atazanavir/ritonavir.**			

Probabilistic sensitivity analyses (PSA) conducted for the base case scenario suggest that the probability that darunavir treatment is cost-effective compared to atazanavir-based treatment is 73.2% at a cost effectiveness threshold of £30,000, and 71.3% at £20,000 per QALY gained. In around 10% of simulations, darunavir treatment was more costly and less effective than atazanavir; and in around 20% darunavir was less costly and less effective than atazanavir. The company noted that there is minimal difference between the two regimens, and small changes in either costs or outcomes could lead to considerable changes in the estimated incremental cost effectiveness ratios.

A wide range of one-way sensitivity analyses have been conducted by the company. The model was most sensitive to variation (within the range of their 95% confidence intervals) in the rate of slow/stable and rapid increases in $CD4^+$ cell count for atazanavir, with cost effectiveness estimates ranging between darunavir having an incremental cost per QALY gained of £2,742, to having an incremental cost saving per QALY foregone of £24,114. The model was next most sensitive to variation in the rate of the slow $CD4^+$ cell count increase for darunavir (estimates ranged from darunavir being dominant over atazanavir, to having an incremental cost saving of £15,326 per

QALY foregone). The majority of other one-way sensitivity analyses indicated that darunavir is dominant.

Lopinavir/ritonavir 400/100mg twice-daily was considered as a comparator in scenario analyses. Assuming lopinavir as the only comparator (100% market share) the incremental cost per QALY gained with darunavir is reported as £43,216, based on an increase in costs of £1,923 and a gain of 0.044 QALYs. The company suggests that the use of lopanavir in Wales is actually low (commercial in confidence data removed), and that atazanavir remains the most appropriate comparator. However, assuming a company-reported market share split between atazanavir and lopinavir (commercial in confidence data removed), darunavir is reported to be the dominant strategy.

4.1.3 AWTTC critique

As noted by the company, the numerical differences in modelled costs and outcomes should be interpreted with caution. There is a lack of robust evidence to support the assumed differences between darunavir and the comparators, and it is plausible that there are no differences in effectiveness and outcomes between the drug regimens. Darunavir acquisition costs are marginally lower than those of atazanavir, and are greater than those of lopinavir.

Strengths of the economic evidence include:

- In the absence of direct comparative data for darunavir and the comparators, a systematic literature review was undertaken to identify relevant trial data and indirect MTC has been undertaken.
- The model structure and use of virological and immunological outcomes to predict effectiveness are well established.
- A wide range of sensitivity and scenario analyses were conducted to address the uncertainty associated with key model parameters.

Limitations of the economic evidence include:

- There is a lack of a direct comparative evidence for darunavir/ritonavir 800/100 mg once-daily and the comparator regimens. The company has acknowledged heterogeneity between studies included in the mixed treatment comparison, in particular with regard to previous antiretroviral treatments received by participants, and there is substantial uncertainty in the resultant relative effectiveness estimates.
- The literature search, performed to identify studies for the mixed indirect comparison was completed at the end of 2009. It is possible that additional studies or longer-term follow ups of discussed studies were not included.
- There is a lack of long term efficacy and safety data for the PIs included in the analysis.
- There is a lack of transparency regarding elements of the non-antiretroviral costs, although these apply to all arms of the model.
- No sensitivity analyses have been conducted around the comparison of darunavir and lopinavir.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of darunavir/ritonavir 800/100 mg once-daily compared to atazanavir/ritonavir 300/100 mg once-daily, or lopinavir/ritonavir 400/100mg twice-daily.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

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5.1 Budget impact evidence

5.1.1 Context and methods

According to the Public Health Wales Surveillance Report[27] there were 1,193 individuals in Wales receiving HIV treatment in 2009. Based on data from 2005–9, the company estimates an average of 157 new individuals will be diagnosed with HIV each year in Wales, with a death rate of 2%. Therefore, the expected net number of HIV patients will approach 1,575 in 2012. Based on company market research, approximately 55% of patients will be antiretroviral treatment-experienced. Further, 89% of these are estimated to have no darunavir resistance and to have viral loads < 100,000 RNA copies/mL and $CD4^+$ counts > 100 cells/mm^3. The number of patients eligible for treatment with darunavir/ritonavir 800/100 mg once-daily is estimated to be 619 individuals in 2012 rising to 806 individuals in 2016. The company anticipates a market share for darunavir of 40% in 2012, rising to 55% in 2016, equivalent to 224 patients to be treated with darunavir in 2012, rising to 391 patients in 2016.

5.1.2 Results of company budget impact analysis

The company estimated that treatment with darunavir/ritonavir 800/100 mg once-daily will cost £4,036 per patient per year, compared to £4,104 for treatment with atazanavir/ritonavir 300/100 mg once-daily. The estimated numbers of patients and the associated cost savings based on displacement of atazanavir over the five year period are summarised in Table 4.

Table 4. Company-reported costs associated with use of darunavir/ritonavir 800/100 mg once-daily compared to atazanavir/ritonavir 300/100 mg once-daily for the treatment of HIV-1 infection in antiretroviral therapy-experienced adults

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	619	667	715	761	806
Uptake	40%	45%	50%	55%	55%
Number of treated patients	224	269	320	374	391
Displaced drug cost per patient	-£67	-£67	-£67	-£67	-£67
Overall net costs	-£14,992	-£18,023	-£21,413	-£25,034	-£26,196

The scenario analyses of resource implications consider switching from different proportions of comparators to darunavir/ritonavir 800/100 mg once-daily, as follows:

- displacement of lopinavir/ritonavir 400/100mg twice-daily (100% lopinavir market share, 0% atazanavir) — additional cost of £561 per patient per year;
- displacement of lopinavir and atazanavir based on relative market share (commercial in confidence data removed) — additional cost of £83 per patient per year.

5.1.3 AWTTC critique of the budget impact analysis

- The company has used available Welsh data to estimate epidemiology of HIV in Wales.
- It is not apparent from the company submission whether darunavir/ritonavir 800/100 mg once-daily is anticipated to displace darunavir/ritonavir 600/100 mg twice-daily. The company did not specify the proportion of the eligible

population in Wales that is currently receiving darunavir/ritonavir 600/100 mg twice-daily.

5.2 Comparative unit costs

Examples of ritonavir-boosted PI regimens (tablets) used in treatment experienced adults with HIV-1 infection are listed in Table 5.

Table 5. Examples of protease inhibitors acquisition costs for the treatment of HIV-1 infection in antiretroviral therapy experienced adults

PI regimen	Example doses	Approximate annual cost
Darunavir/ritonavir	Darunavir 800 mg/ritonavir 100 mg od	£3,860
	Darunavir 600 mg/ritonavir 100 mg bid	£5,908
Atazanavir/ritonavir	Atazanavir 300 mg/ritonavir 100 mg od	£3,927
Lopinavir/ritonavir	Lopinavir 400 mg/ritonavir 100 mg (as Kaletra®) bid	£3,472
Fosamprenavir/ritonavir	Fosamprenavir 700 mg/ritonavir 100 mg bid	£3,624
Saquinavir/ritonavir	Saquinavir 1000 mg/ritonavir 100 mg bid	£3,530
Tipranavir/ritonavir*	Tipranavir 500 mg/ritonavir 200 mg bid	£6,312

od: once-daily; bid: twice-daily.
*Tipranavir is licensed only for highly treatment-experienced patients with virus resistant to multiple PIs.
See relevant Summaries of Product Characteristics for full dosing details.
Costs are based on MIMS [28] list prices as of 6 March 2012, and assumption of 365 days of treatment.
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that darunavir is appropriate for specialist only prescribing within NHS Wales for the stated indication.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

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Appendix 1. Additional clinical information

Table A1: Summary of key trials used in the mixed treatment comparison

Study	Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
ODIN Cahn, P et al. AIDS 2011; 25: 929-35	Phase III, 48 week open-label trial. Initial 4 week screening period, followed by 48 week treatment period and 4 week follow up. Patients stratified on basis of screening viral loads (≤ 50,000 RNA copies/mL or > 50,000 RNA copies/mL. Treatment groups: • 600 mg darunavir/100 mg ritonavir bid (bid group) • 800 mg darunavir/100 mg ritonavir od (od group)	Inclusion criteria: • Male or female > 18 years • Documented HIV-1 infection • Receiving a stable HAART regimen for at least 12 weeks at screening • HIV-1 RNA > 1000 RNA copies/mL at screening • No darunavir RAMs • Informed consent given Exclusion criteria: • Presence of active conditions fitting AIDS except Kaposi sarcoma or wasting syndrome • Previous/current use of enfuviritide or tipranavir, with or without darunavir • Life expectancy < 12 months • Pregnant or breast feeding • Other active disease affecting safety or outcome	n = 590; all treatment experienced patients. bid: n = 296 od: n = 294 Males bid: 60.9% od: 66.9% Caucasians bid: 34.7% od: 37.2% Mean age, years (SE) bid: 40.2 (0.53) od: 40.7 (0.55) Mean baseline viral load: 4.16 $\log_{10}$ RNA copies/mL Median baseline $CD4^+$ count: 228 cells/µL	Primary outcome: • virologic response defined as viral load < 50 RNA copies/mL at week 48 Secondary outcome: • change in $CD4^+$ count from baseline at week 48 • safety profile **Key results** • At week 48, 72.1% of od and 70.9% bid patients had viral load < 50 RNA copies/mL • Mean $CD4^+$ counts had increased by 100 (od) and 94 (bid) • Virologic failure was low in both arms (22.1% od, 18.2% bid) • 1 patient developed a protease inhibitor mutation (from the od group) • od group had lower incidence of elevated triglycerides than bid group. • Data are taken to show that darunavir/ritonavir given as 800 mg/100 mg od is non-inferior to 600 mg/100 mg taken bid. *Safety*: **Adverse event** / **od** / **bid** ≥ 1 grade 1/2 event: 75.5% / 75.7% Serious adverse event: 5.4% / 9. 1% Grade 3/4 event: 7. 8% / 15. 2% Deaths: 2 + 1* / 6 Nausea: 10.9% / 10.5% Vomiting: 3.1% / 5.4% Diarrhoea: 9.9% / 15.2% Rash: 2.7% / 2.7% Headache: 1.4% / 2.0% Trig > 500 mg/dL: 5.2% / 11.0% Chol > 240 mg/dL: 10.1% / 20.6% ALT, AST >5 x ULN: 3.8% / 7.0% * 1 death post discontinuation. No deaths directly related to treatment.

Table A1: Summary of key trials used in the mixed treatment comparison

Study	Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
POWER 1 Katlama C et al. Future HIV Therapy 2008; 2: 229-45	144 week phase IIb randomised control trial. Patients stratified by number of protease inhibitor mutations, enfuviritide use and baseline viral load. Treatment regimens • Darunavir/ritanovir 400 mg/100 mg od • Darunavir/ritonavir 800 mg/100 mg od • Darunavir/ritonavir 400 mg/ 100 mg bid • Darunavir/ritonavir 600 mg/ 100 mg bid • Control group of investigator selected protease inhibitors (amprenavir, atazanavir, lopinavir or sequinavir) Above plus investigator-selected OBR (≥ 2NRTI with or without enfuviritide) based on genotypic resistance and treatment history. After 24 weeks of dose-finding and primary efficacy studies all darunavir patients were switched to 600/100 mg bid dosing.	Inclusion criteria: • Male and female > 18 years • Highly ART-experienced patients • Documented HIV-1-infected adults • Viral load > 1000 RNA copies/mL • ≥ 1 protease inhibitor mutation on screening • Stable protease inhibitor regimen for at least 8 weeks before study • Prior use of ≥ 1 NRTI for at least 3 months • Use of ≥ 1 NNRTI as part of failing regimen • Informed consent given Exclusion criteria: • Presence of AIDS-defining illness • Past/current history of alcohol or drug abuse with potential to affect safety • Any NNRTI as part of treatment at screening • Any interruption of treatment at screening • Hepatitis A, B or C infection. • Patient on investigational ART as part of treatment at screening or up to 90 days prior.	See POWER 1& 2 analysis	See POWER 1& 2 analysis

Table A1: Summary of key trials used in the mixed treatment comparison

Study	Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
POWER 2 Clotet B et al Lancet 2007; 569: 1169-1178	144 week phase IIb randomised control trial. Dose groups as for POWER 1	Inclusion criteria: • Male and female > 18 years • Highly ART-experienced patients • Documented HIV-1-infected adults • Viral load > 1000 RNA copies/mL • ≥ 1 protease inhibitor mutation on screening. • Stable protease inhibitor regimen for at least 8 weeks before study • Prior use of ≥ 1 NRTI for at least 3 months • Use of ≥ 1 NNRTI as part of failing regimen • Informed consent given Exclusion criteria: • As POWER 1 plus. • Lab evidence of liver disease (AST, ALT > 2 x ULN; Total bilirubin > 1.5 x ULN • Haemoglobin < 7.9 g/dL • Platelets < 75000/mm^3 • Neutrophils < 999 mm^3 • Creatinine > 1.5 x ULN • Lipase > 1.5 x ULN	See POWER 1& 2 analysis	See POWER 1& 2 analysis

Table A1: Summary of key trials used in the mixed treatment comparison

Study	Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
POWER 1&2 Analysis Clotet B et al Lancet 2007; 569: 1169-1178	See above	See above	n = 254 • 124 Control treatment (C) • 131 Darunavir/ritonavir (D/r) patients Males C: 88% D/r: 89% Caucasians C: 73% D/r: 81% Mean age, years (SD) C: 44.4 (7.1) D/r: 43.9 (8.6) Mean duration of infection, years (SD) C: 12.9 (4.9) D/r: 12 (4.4)	Primary end-point • Confirmed viral load reduction of ≥ 1 log_{10} RNA copies/mL from baseline by week 24 Secondary end-points • Proportion of patients achieving viral loads of less than 50 and 400 RNA copies/mL • Change in viral load from baseline • Change in $CD4^+$ count from baseline Safety and tolerability were also assessed. **Results – D/r 800/100 mg od vs D/r 600/100 mg bid vs. control** <u>Baseline</u>: D/r (800/100) D/r (600/100) Control N 23 29 28 % male 74 69 82 Mean VL (RNA copies/mL) 4.51 4.47 4.14 Median $CD4^+$ count ($cells/mm^3$) 96 162 228 <u>24 weeks:</u> D/r (800/100) vs. D/r (600/100) vs. Control *Proportion with VL < 50 RNA copies/mL* 67% 62% 11% *Change in VL from baseline* $-2.39log_{10}$ $-2.35log_{10}$ $-0.68log_{10}$ *Mean $CD4^+$ count increase* 88 111 33

Table A1: Summary of key trials used in the mixed treatment comparison

Study	Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
POWER 1&2 Analysis Continued				**Results – D/r 600/100 mg bid versus control** <u>24 weeks</u> *Reduction in viral load ≥ 1 log_{10}* D/r (600/100) Control POWER 1 77% 25% POWER 2 62% 14% *Proportion with VL < 50 RNA copies/mL* D/r (600/100) Control POWER 1 53% 18% POWER 2 39% 7% *Proportion with VL < 400 RNA copies/mL* D/r (600/100) Control POWER 1 67% 25% POWER 2 49% 10% *Mean change in $CD4^+$ counts ($cells/mm^3$)* D/r (600/100) Control POWER 1 124 20 POWER 2 75 12 <u>48 weeks</u> *Reduction in viral load ≥ 1 log_{10}* D/r (600/100) Control POWER 1+2 61% 15% *Proportion with VL < 50 RNA copies/mL* D/r (600/100) Control POWER 1+2 45% 10% *Proportion with VL < 400 RNA copies/mL* D/r (600/100) Control POWER 1+2 54% 13% *Mean change in $CD4^+$ counts ($cells/mm^3$)* D/r (600/100) Control POWER 1+2 102 19

Table A1: Summary of key trials used in the mixed treatment comparison

Study	Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
TITAN Valdez Madruga et al Lancet 2007; 370: 49-58	Open-label 96 week phase III trial of darunavir/ritonavir versus lopinavir/ritonavir in early treatment-experienced patients naïve to lopinavir. Patients selected to have less advanced disease than subjects in POWER trials. Dosing: Darunavir/ritonavir (D/r) 600/100 mg bid Lopinavir/ritonavir (L/r) 400/100 mg bid (although those on NNRTIs received 533/133 mg or 600/150 mg depending on whether on capsules or tablets as per prescribing guidelines). OBR selected by investigator but containing at least 2 NRTI, and with/without NNRTI (excluding enfuvuritide and investigational products). Randomisation by permuted blocks and stratified by +/- NNRTI and RNA levels (< 50000 RNA copies/mL or ≥50000 RNA copies/mL).	Inclusion criteria: Treatment experienced HIV-1 infection ≥ 18 years RNA concentration > 1000 RNA copies/mL HAART treatment ≥ 12 weeks Informed consent Exclusion critera: Previous exposure to lopinavir, darunavir, tipranavir, enfuviritide or investigational antiretrovirals Hepatitis B or C unless clinically stable Clinical AIDS-related conditions except stable Kaposi's sarcoma and wasting syndrome	n = 595 • D/r: 298 • L/r: 297 Males: • D/r: 77% • L/r: 81% Mean age, years (SD): • D/r: 40.9 (9.0) • L/r: 40.8 (8.6) Caucasian: • D/r: 54% • L/r: 57% Mean duration of infection (SD) D/r: 9.1 (5.5) L/r: 9.1 (5.8) Mean baseline log_{10} RNA (SD) D/r: 4.33 (0.79) L/r: 4.28 (0.81) Median $CD4^+$ count (cells/μL) [range] D/r: 235 [3 – 831] L/r: 230 [2 – 1906]	Primary outcome: • The proportion of patients with confirmed RNA level < 400 RNA copies/mL at week 48 Secondary outcomes: • Proportion of patients with RNA < 50 RNA copies/mL • Proportion with at least 1.0 log_{10} RNA reduction from baseline • Mean change in log_{10} RNA at all time points • Median change in $CD4^+$ cell count • Time to loss of virological response algorithm used to assess virological response at < 400 and < 50 copes/mL levels. Results Proportion with RNA levels < 400 RNA copies/mL at week 48 D/r: 77% L/r: 67% Least mean square difference: 9%. Confidence interval does not include 0: proof of non-inferiority and suggests D/r superior to L/r Proportion with RNA levels < 50 RNA copies/mL at week 48 D/r: 71% L/r: 60% Proportion with reduction in RNA copies of at least log_{10} at week 48 D/r: 77% L/r: 69%

Table A1: Summary of key trials used in the mixed treatment comparison

Study	Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
TITAN Continued				Results (continued) Mean change in RNA load from baseline at week 48 D/r: -1.95 log_{10} L/r: -1.72 log_{10} Median $CD4^+$ count change from baseline at week 48 D/r: 88 cells/μL L/r: 81 cells/μL More L/r patients had a loss of susceptibility to protease inhibitors and NRTIs through mutations than did D/r patients. Safety: No new safety signals detected. Most adverse events were mild and included headache, nausea, diarrhoea and nasopharyngitis. Rashes were seen in 16% of D/r patients and 7% L/r patients. Approximately twice as many grade 2-4 adverse events noted for L/r than D/r.

Table A1: Summary of key trials used in the mixed treatment comparison

Study	Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
BMS-045 Johnson M et al AIDS 2005; 19: 685 - 94	Randomised open-label 48-week multicentre trial. Treatment groups Atazanavir/ritonanvir (A/r) 300/100 mg od Atazanavir/saquinavir (A/s) 400/1200 mg od Lopinavir/ritonavir (L/r) 400/100 mg bid In first 2 weeks of study existing NRTI maintained and failing NNRTI/PI switched to new randomised treatment After 2 weeks, NRTI switched to tenofovir plus one other depending on resistance testing	Inclusion criteria: Male, female > 16 years Not pregnant Previously failed ≥2 HAART regimens that included ≥ 1 NRTI, an NNRTI and a PI. Baseline viral load ≥1000 RNA copies/mL Baseline $CD4^+$ count ≥ 50 cells/µL Previously responded to ≥ 1 HAART regimen with a decrease in viral load by 1 log_{10} or to < 400 RNA copies/mL Exclusion criteria: Creatinine > 1. 5 x ULN Total bilirubin > 1. 5 x ULN Lipase > 1. 4 x ULN ALT, AST > 3 x ULN Previous use of atazanavir, lopinavir/ritonavir or tenofovir for more than 30 days, or saquinavir for more than 30 days unless phenotyping revealed continued sensitivity.	All PI-experienced n = 358 A/r: n = 120; A/s: n = 115; L/r: n = 123 Males: A/r: 80%; A/s: 77%; L/r: 78% Mean age, years (SE) A/r: 41 (0.8); A/s: 42 (0.8); L/r: 40 (0.7) Caucasians A/r: 63%; A/s: 61%; L/r: 58% Median HIV count log_{10} (RNA copies/mL) A/r: 4.44; A/s: 4.42; L/r: 4.47 Median $CD4^+$ count (cells/µL) A/r: 317; A/s: 286; L/r: 283	Primary end point: Comparison to L/r arm to prove non-inferiority of other treatments in terms of time-average difference over 48 weeks. Secondary end points: Percentages of patients with viral load < 400 RNA copies/mL and < 50 RNA copies/mL in intention-to-treat and as-treated subjects/ Safety end points Serious adverse effects and deaths. Results: Time-averaged differences: A/r vs L/r: 0.13 [-0.12, 0.39] A/s vs. L/r: 0.33 [0.07, 0.60] Mean change in viral load from baseline A/r: -1.93 A/s: -1.55 L/r: -1.87 % responding to treatment by viral load (intent-to-treat) VL < 400 RNA copies/mL — VL < 50 RNA copies/mL A/r 56 38 A/s 38 26 L/r 58 46 % responding to treatment by viral load (as-treated) VL < 400 RNA copies/mL — VL < 50 RNA copies/mL A/r: 71 52 A/s: 53 38 L/r: 66 54

ALT: alanine transaminase. **ART**: anti-retroviral therapy. **AST**: aspartate transaminase. **bid**: twice-daily. **Chol**: cholesterol. **γGT**: gamma-glutamyl transferase. **HAART**: highly active anti-retroviral therapy. **NRTI**: nucleoside-analogue reverse transcriptase inhibitor. **NNRTI**: non-nucleoside-analogue reverse transcriptase inhibitor. **OBR**: optimised background regimen. **PI**: protease inhibitor. **Pt**: patient **od**: once-daily **SD**: standard deviation. **SE**: standard error. **Trig**: triglycerides. **Tx**: treatment. **ULN**: upper limit of normal **VL**: viral load (copies RNA/mL)

Appendix 2. Additional health economic information

Table A2. Health economic model detail

	Base case model	Appropriate?
Comparator(s)	The base-case cost-utility analysis presented in the company submission[1] compares darunavir 800 mg co-administered with ritonavir 100 mg once-daily compared to atazanavir 300 mg co-administered with ritonavir 100 mg once-daily. Scenario analyses also include comparison with lopinavir 400 mg co-administered with ritonavir 100 mg twice-daily.	Yes, as agreed with AWTTC. Due to the estimated low use of lopinavir in Wales (commercial in confidence data), the company chose atazanavir as the major comparator. Scenario analyses also include comparisons according to relative market share at the time of submission (commercial in confidence data removed).
Population	The model population includes adults with HIV-1 infection and previous antiretroviral therapy-experience with no darunavir resistance associated mutations and who have plasma HIV-1 RNA <100,000 RNA copies/mL and $CD4^+$ cell count ≥100 cells/mm³. Population characteristics have been derived from the ODIN trial. Sensitivity and scenario analyses address variation in age and gender distributions.	Yes, reflects the darunavir licensed indication under appraisal. Based on company market research, 89% of treatment-experienced HIV-1 patients have no darunavir resistance associated mutations, and have plasma HIV-1 RNA < 100,000 copies/mL, and a $CD4^+$ cell count ≥ 100 cells/mm³. Of note, neither atazanavir nor lopinavir use is restricted to use in patients with plasma HIV-1 RNA < 100,000 copies/mL, and a $CD4^+$ cell count ≥ 100 cells/mm³. The base case model employs data from the ITT populations enrolled in the comparator trials, rather than the subgroup of patients meeting the darunavir licensed indication.
Model type and description	Cost-utility analysis (CUA), based on Markov model. The model assumes six health states correspondent to different $CD4^+$ cell count ranges (> 500, 351–500, 201–350, 101–200, 51–100 and 0–50 cells/mm^3), and one absorbing state (death). The model defines three levels of virologic response: complete suppression (< 50 RNA copies/mL), partial suppression (from 50 to 1−$\log_{10}$ RNA copies/mL drop) and no suppression (< 1-$\log_{10}$ RNA copies/mL drop). For each virologic response category the model assumes three time periods of $CD4^+$ count changes: an initial period of rapid increase in $CD4^+$ count, followed by a period of either slowly changing or stable $CD4^+$ cell count, followed by a period of declining $CD4^+$ cell count. The model assumes up to three lines of treatment regimens. The patients are allowed to switch treatment either after virologic failure or after a period of declining $CD4^+$ cell count.	Yes, CUA is appropriate. The company has adapted its previous darunavir models to analyse the cost-effectiveness of darunavir treatment in its new licensed indication. Due to the wide range of optimized drug regimens for treatment-experienced HIV-1 patients, the subsequent lines of therapy were informed by expert opinion.

Table A2. Health economic model detail

	Base case model	Appropriate?
Perspective	NHS Wales.	Appropriate. The analysis considers direct medical costs from the perspective of NHS Wales.
Time horizon	Analysis assumes a life-time horizon. Sensitivity analyses have been conducted for 10 and 15 years.	Appropriate. Sensitivity analyses using 10 and 15 year time horizon demonstrates that darunavir therapy dominates atazanavir therapy.
Discount rate	A 3.5% p.a. discount rate is applied to both costs and outcomes. Scenario analyses include discount rates of 0% and 6%.	Appropriate.
Efficacy	Clinical outcomes used in the model included virologic response rates (plasma HIV-1 RNA) and immunologic response rates ($CD4^+$ cell counts) at 24 weeks. The percentage of patients in each virologic response category was derived from an indirect mixed treatment comparison (MTC). The rates of change of $CD4^+$ cell counts are based on data between 24 and 48 weeks, with durations of treatment drawn from the published literature on sustainability of immunological responses. HIV-related mortality rates were estimated by $CD4^+$ cell count using a published study[29]. Gender and age-specific non-HIV mortality rates were taken from UK National Statistics (2010).	Due to the lack of direct comparative data for darunavir 800mg co-administered with ritonavir 100mg once-daily and comparator treatments, the company has undertaken a systematic review of relevant trial data with which to conduct an indirect MTC. The proportion of darunavir recipients that achieved viral loads < 50 copies/ml at 24 weeks was estimated to be lower in the MTC than was observed in the ODIN trial; therefore the ODIN clinical trial data provide the virological response data for darunavir and the estimates for atazanavir obtained from the MTC are reported to be adjusted upwards by the ratio of the darunavir estimates from the ODIN trial and MTC. The company acknowledges that there is heterogeneity among the clinical trials included in the MTC, particularly in relation to prior treatment experience. There were no statistically significant differences observed between darunavir and the comparators in virological and immunological responses in the MTC, and the credible intervals around the point estimates are wide, reflecting the limited evidence. The base case model uses point estimates of virological response which numerically favour darunavir, and point estimates of immunological response which numerically favour the comparators. However, it is plausible that there are no differences in these outcomes between darunavir and the comparators. In addition, the

Table A2. Health economic model detail

	Base case model	Appropriate?
		model uses virological and immunological data for the comparator trials that are based on wider ITT populations than the subpopulation licensed to receive darunavir, although sensitivity analysis restricting the comparator populations to those with HIV-1 RNA <100,000 copies/mL and $CD4^+$ cell count ≥100 cells/mm³ appears to support the conclusions of the base case model. The duration of therapy (determined by the initial period of rapid increase and the slower/stable period of $CD4^+$ cell counts) is assumed to be 0.25 years longer for darunavir recipients who achieved viral suppression to < 50 RNA copies/mL compared with atazanavir recipients, although this would seem to be a further source of uncertainty. As for all PIs considered in the current analysis, data on long term outcomes are lacking. Collectively, the key parameters driving the model outputs are based on assumptions and limited supporting evidence. Sensitivity analyses demonstrate that the model is most sensitive to assumed rates of $CD4^+$ changes and durations of the slow/stable $CD4^+$ periods.
Adverse effects	Adverse effects were not included in the analysis, as adverse event profiles were considered by the company to be similar for darunavir and atazanavir, based on data from the MTC.	There is lack of long-term safety data for darunavir 800 mg co-administered with ritonavir 100 mg once-daily, and the comparators.

Table A2. Health economic model detail

	Base case model	Appropriate?
Utility values	Utility values stratified by $CD4^+$ cell counts used in the model were derived from a USA study[30] HR-QoI data were collected using the self-reported EQ-5D questionnaire.	Utility values used in the model are drawn from a published cost effectiveness analysis of lopinavir conducted in the USA[30]. Utilities reported in this study are based on 21,000 clinical trial HIV patient responses measured by the EuroQol quality of life instrument (EQ-5D). These utility value data have been used in several previous models of HIV, although the actual weights appear to be higher than those estimated as the average UK population norms for EQ-5D[31]. Darunavir remained the dominant treatment strategy when utility values were explored within assumed ranges based on other published estimates.
Resource use and costs	The costs of antiretroviral therapy for the first and subsequent lines of therapy were derived using a micro-costing approach conducted by the company based on the ODIN trial. Other treatment-related costs were derived from a UK HIV database (2000-2006) using the approach described in a study by Petrou et al (1996)[32].	Resource use estimations used in the model are not transparent and are based on dated sources with costs uplifted to 2011 values. It is unclear whether all relevant costs (e.g. genotype resistance tests) have been included in the model, although these would apply equally to all comparators.
Uncertainty	A wide range of one-way sensitivity analyses have been conducted to address the uncertainty associated with key parameters for the comparison of darunavir and atazanavir, including duration of $CD4^+$ count changes and virologic response; costs of second and third line therapies; age and gender distributions; utility values; baseline $CD4^+$ distribution; and mortality. Scenario analyses included lopinavir as a comparator (100% market share) and lopinavir and atazanavir as a comparator (commercial in confidence data removed); variation in gender (100% men, 50% men, 100% women), age (15-39; 40-64, 65+ years); time horizon (10 and 15 years); discount rate (0% and 6%); starting $CD4^+$ cell count, and responses to darunavir and atazanavir treatments (viral load and $CD4^+$ cell count).	Considered appropriate for the comparison of darunavir and lopinavir. Sensitivity analyses demonstrate that the model is sensitive to the rates of change in $CD4^+$ counts and duration of treatment with darunavir and the comparators. The company notes that the modelled costs and outcomes are very similar and that any differences in ICERs arising from small changes in either should be interpreted with caution. No sensitivity analyses have been presented for the comparison of darunavir against lopinavir.
Model provided?	Yes.	Appropriate.