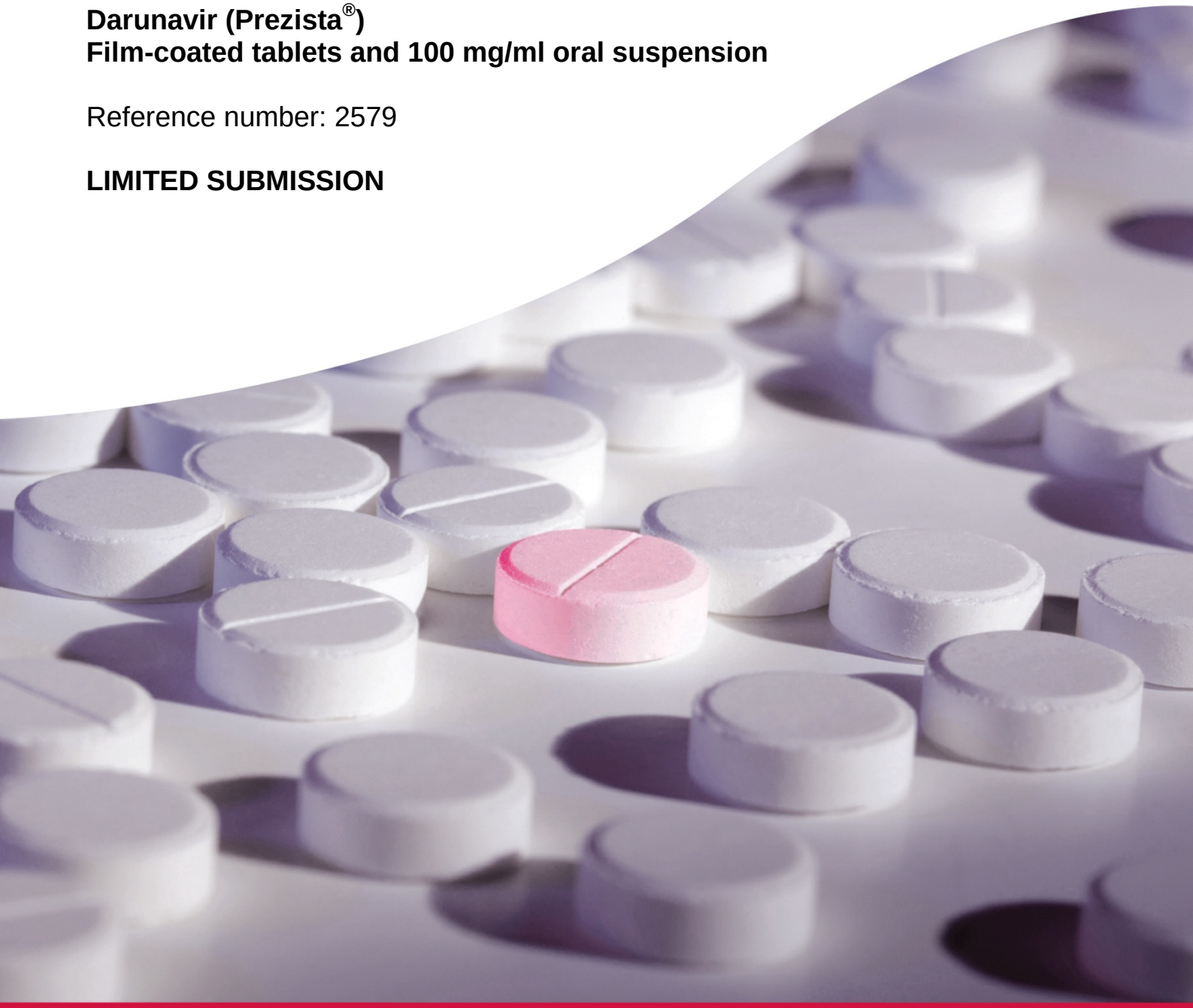
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Darunavir (Prezista®)
Film-coated tablets and 100 mg/ml oral suspension

Reference number: 2579

LIMITED SUBMISSION



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AWMSG ADVICE FOR DARUNAVIR (PREZISTA®) IN PAEDIATRIC PATIENTS FROM THE AGE OF THREE YEARS AND AT LEAST 15 KG

LICENCE

Darunavir (Prezista®) co-administered with low dose ritonavir is licensed in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in paediatric patients from the age of three years and at least 15 kg body weight.

OVERVIEW

In October 2014 darunavir received a licence extension to include once daily use in children aged 3 to 12 years ≥ 15 kg who are treatment-naive, or in treatment-experienced children with no DRV-RAMs and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/l.

The company has submitted evidence for this license extension and this is presented in the AWMSG secretariat report (ASAR).

The All Wales Medicines and Strategy Group (AWMSG) has previously recommended the following as an option for the use of darunavir in children and adolescents:
Twice daily dosing:

- Co-administered with low dose ritonavir, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced children and adolescents from the age of 6 years and at least 20 kg body weight. This recommendation pre-dated marketing authorisation of a once-daily dose of darunavir[1].
- 100 mg/ml oral suspension, co-administered with low dose ritonavir for use in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in ART-experienced paediatric patients from the age of 3 years and at least 15 kg body weight[2].

Once-daily dosing:

- Treatment of HIV-1 infection in paediatric patients from the age of 12 years and at least 40 kg body weight who are: ART-naive; or ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/l (see reference[3]).

A literature search by the All Wales Therapeutics and Toxicology Centre (AWTTC) did not provide any additional evidence which would affect the existing AWMSG recommendations for the use of darunavir in paediatric patients.

AIM

1. To appraise darunavir for the licence extension as a limited submission
2. Consider previous advice for the use of darunavir in children and adolescents
3. Issue a single piece of advice for the use of darunavir (Prezista®) co-administered with low dose ritonavir for the treatment of HIV-1 infection in paediatric patients from the age of 3 years and at least 15 kg body weight. This will provide greater clarity within NHS Wales.

AWMSG Secretariat Assessment Report
Darunavir (Prezista®) film-coated tablets and 100 mg/ml oral suspension

This assessment report is based on evidence from a limited submission by Janssen-Cilag Ltd on 5 February 2015[4].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Darunavir (Prezista®) once-daily, co-administered with low dose ritonavir in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in paediatric patients aged 3 years to < 12 years and at least 15 kg body weight who are: ART-naive; or ART-experienced with no DRV-RAMs and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/l (see reference[5]).
Dosing	The recommended dose of darunavir is 600 mg (≥ 15 kg to < 30 kg), 675 mg (≥ 30 kg to < 40 kg) and 800 mg (≥ 40 kg) in combination with 100 mg ritonavir once-daily taken with food. Refer to the Summary of Products Characteristics (SPC) for further information regarding dosing[6–8].
Marketing authorisation date	Licence extension granted on 30 October 2014[9] (first licensed for use in the paediatric population on 23 June 2009[9]).
Comparators	Atazanavir (Reyataz®) with ritonavir (Norvir®) Lopinavir/ritonavir (Kaletra®).
Limited submission details	Darunavir (Prezista®) met the following criteria for eligibility for a limited submission: • A minor licence extension. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparator(s).

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

To support the licence extension the company provided evidence from a two week substudy and results from model-based pharmacokinetic simulations of darunavir/ritonavir in children, adolescents and adult patients [4,5].

2.1 Supporting evidence

The main objective of the substudy of TMC114-C228 was to evaluate the pharmacokinetics of a once daily dose of darunavir/ritonavir at steady-state in HIV-1 infected children. The substudy was a two week analysis of ten treatment-experienced children with HIV-1 infection, aged 3 years to < 6 years[4,5]. Patients who had been receiving darunavir/ritonavir twice daily for 32 weeks and had undetectable plasma viral load (< 50 HIV-1 RNA copies /ml) after 24 weeks were changed to once daily darunavir/ritonavir for two weeks. Patients continued to receive their optimised background antiretroviral treatments from the main study during the substudy. Three patients had body weights < 15 kg and seven weighed ≥ 15 kg and, based on

pharmacokinetic modelling received doses of 560/96 mg and 600/96 mg darunavir/ritonavir respectively[4,5]. Results from the paediatric population pharmacokinetic analysis indicated that darunavir exposure was comparable to that observed in treatment-naive and treatment-experienced adults with no DRV RAMs when treated with darunavir/ritonavir 800/100 mg once daily[5]. In addition HIV levels in all patients in the substudy remained undetectable after two weeks of once daily darunavir/ritonavir dosing[4,5].

Pharmacokinetic data from the substudy of TMC114-C228 in children aged 3 years to < 6 years and study TMC114-C230, conducted using once daily darunavir/ritonavir in ART-naive patients aged from 12 years to < 18 years (40–65 kg) were used to update the overall darunavir population pharmacokinetic model. This model was then used to simulate dosing regimens for once daily dosing of darunavir in combination with ritonavir for paediatric patients from 3 to < 12 years and weighing ≥ 15 kg[4,5]. The Committee for Medicinal Products for Human Use (CHMP) were satisfied that based on the clinical studies of once daily dosing in 3 to < 6 year and 12 to < 18 year old patients and data from the updated population pharmacokinetic model that the proposed once daily dosing regimens of darunavir in combination with ritonavir could be considered for treatment-naive and treatment-experienced paediatric patients without DRV-RAMs[5]. CHMP noted that a once daily dose regimen results in comparable darunavir exposure in paediatric patients to that observed in adults allowing the extrapolation of safety and efficacy.

Evaluation of the short term safety and tolerability of darunavir/ritonavir was a secondary objective of the substudy. The safety data did not give rise to any new clinically relevant findings compared with the known darunavir/ritonavir safety profile[5].

2.2 Points to note

- No comparative clinical evidence for the use of darunavir versus atazanavir or lopinavir was included in the company submission. There are differences in the licensed ages for the comparator products; lopinavir is licensed from two years of age and atazanavir from six years of age.
- Data to support use in patients aged 6 to < 12 years were based on pharmacokinetic studies only and the substudy of TMC114-C228 in children 3 to < 6 years had very low patient numbers; there are therefore very limited pharmacokinetic, clinical efficacy and safety data for the paediatric population of interest. However CHMP noted that based on the identification of suitable dose regimens and the expectation that pharmacokinetic relationships are the same in children and adults, the extrapolation of efficacy data obtained in adults to children may be accepted[5].
- Once-daily darunavir/ritonavir may improve adherence compared with twice-daily regimens.

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company state that there are 12 paediatric patients infected with HIV-1 in Wales, of which 5 are estimated to be between the ages of 3 and 12 years[10]. Due to the relatively low incidence of HIV in Wales the company assume that the patient pool will remain constant over the next five years. Based on a company estimated market share of protease inhibitors of 30–37% and a mean annual medicine cost of darunavir per patient of £3,371, the company estimate a budget impact of £6,743 (two patients) annually for 2015 and 2016 and £3,371 (one patient) annually for 2017–2019[4].

3.1.1 AWTTC critique

- The company has used an annual cost per patient based on an average cost of tablet use in patients with weights of ≥ 15 kg to 30 kg, ≥ 30 kg to 40 kg and > 40 kg which may not be reflective of the distribution of weight in clinical practice. The company's cost per patient is based on the use of darunavir in combination with 100 mg ritonavir tablets and does not account for usage of ritonavir solution, which if used in place of ritonavir tablets, would lead to higher average annual costs.
- The company has made assumptions of the market share of protease inhibitors which cannot be verified. In addition the company has assumed 100% uptake which may not be the case in clinical practice.
- Despite being subject to some uncertainty, the net budget impact of darunavir for the licensed extension, if approved, is likely to be low.

3.2 Comparative unit costs

Table 1 provides comparative annual acquisition costs of darunavir (Prezista®) in combination with ritonavir (Norvir®), lopinavir/ritonavir (Kaletra®) and atazanavir (Reyataz®) in combination with ritonavir.

Table 1. Examples of acquisition costs for darunavir/ritonavir and comparators for the treatment of HIV-1 infection in paediatric patients in combination with other antiretroviral medicines

Medicine	Example regimen		Cost per year†	
	3 year old	12 year old††	3 year old	12 year old
Darunavir (Prezista®) plus **ritonavir (Norvir®) once daily***	600 mg (6ml) darunavir plus 100 mg (1.2 ml) ritonavir	675 mg darunavir plus 100 mg ritonavir	£3,112	£3,296
Darunavir (Prezista®) plus **ritonavir (Norvir®) twice daily****	380 mg (3.8 ml) darunavir plus 50 mg (0.6 ml) ritonavir	450 mg darunavir plus 60 mg ritonavir	£3,837	£4,570
Lopinavir/ritonavir (Kaletra®) twice daily	150 mg lopinavir/37.5 mg ritonavir (1.9 ml)	400 mg lopinavir/100 mg ritonavir	£1,422	£3,743
Atazanavir (Reyataz®) plus **ritonavir (Norvir®) once daily**¶**	n/a	200 mg atazanavir plus 100 mg ritonavir	n/a	£2,084

†costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of 25 February 2015[11]
n/a = not applicable
*for patients.who are ART-naive or ART-experienced with no DRV-RAMs
**for patients who are not eligible for once daily dosing
¶for patients ≥ 6 years
††based on a child weighing 39 kg
Refer to the SPCs for full dosing details[6–8,12–17]

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, darunavir (Prezista®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that 25% of darunavir (Prezista®) in this patient population may be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 19 March 2015.
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

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16 AbbVie Ltd. Norvir® 80 mg/ml oral solution. Summary of Product Characteristics. Dec 2014. Available at: http://www.medicines.org.uk/emc/medicine/6032. Accessed Mar 2015.
17 Bristol Myers Squibb Pharmaceutical Ltd. Reyataz® 150 mg, 200 mg and 300 mg hard capsules. Summary of Product Characteristics. Dec 2014. Available at: http://www.medicines.org.uk/emc/medicine/14145. Accessed Feb 2015.

Appendix: Previous AWMSG secretariat assessment report (published April 2014)

In April 2014 AWMSG appraised Darunavir (Prezista®) for the treatment of (human immunodeficiency virus-1 (HIV-1) infection in paediatric patients from the age of 12 years and at least 40 kg body weight who are: antiretroviral therapy (ART)-naive; or ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106 /l.) (AWTTC reference number 2246). This advice is now incorporated into the Final Appraisal Recommendation (FAR) of Darunavir (Prezista®) for the treatment of (human immunodeficiency virus (HIV-1) infection in paediatric patients from the age of three years and at least 15 kg body weight. (AWTTC reference number 2579).

The original report for AWTTC reference number 2246 is included below for completeness.

AWMSG Secretariat Assessment Report
Darunavir (Prezista®) 400 mg and 800 mg film-coated tablets and 100 mg/ml oral suspension

This assessment report is based on evidence from a limited submission by Janssen-Cilag Ltd on 29 November 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Darunavir (Prezista®) once-daily co-administered with low dose ritonavir in combination with other antiretroviral medicinal products is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in paediatric patients from the age of 12 years and at least 40 kg body weight who are: antiretroviral therapy (ART)-naive; or ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and $CD4^+$ cell count ≥ 100 cells x 10^6/l. In deciding to initiate treatment with darunavir in such ART-experienced patients, genotypic testing should guide the use of darunavir[2,3].
Dosing	The recommended dose for darunavir in ART-naive and -experienced paediatric patients aged between 12 to 17 years and weighing at least 40 kg is 800 mg once-daily (one 800 mg tablet or two 400 mg tablets can be used to construct the once-daily regimen) in combination with 100 mg ritonavir once-daily taken with food. Darunavir must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. For patients who are unable to swallow tablets, darunavir is also available as an oral suspension. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2,3].
Marketing authorisation date	Licence extension granted on 19 September 2013[4] (licensed for the treatment of HIV-1-infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor (PI) 12 February 2007)[2,3,5].
Comparators	The company submission includes evidence of the effectiveness and safety of darunavir in adult patients[1].
Limited submission details	Darunavir (Prezista®) for the above indication met the following criteria for eligibility for a limited submission: • A minor licence extension. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

In order to support the use of once-daily darunavir for the licensed indication under consideration, the company submission provides evidence for the use of once-daily darunavir in ART-naive HIV-1-infected paediatric patients (DIONE study; TMC114-C230), and also data from the ARTEMIS (TMC114-C211) and ODIN (TMC114-C229)

studies, evaluating the use of darunavir in treatment-naive and treatment-experienced adults, respectively.

2.1 Treatment-naive adolescents

The DIONE (TMC114-C230) study was a phase II, 48-week, multicentre open-label trial which investigated the efficacy, safety, tolerability and pharmacokinetics of once-daily darunavir 800 mg plus ritonavir 100 mg (DRV/rtv 800 mg/100 mg) in combination with an investigator-selected background regimen (consisting of either zidovudine/lamivudine or abacavir/lamivudine) in treatment-naive, HIV-1-infected adolescents aged 12 to < 18 years (n = 12; 8 female and 4 male; mean age of 14.6 years)[1,6,7].

The study consisted of three phases, starting with a screening phase of 4 weeks, treatment phase of 48 weeks and a follow-up period of 4 weeks to report any adverse events (AEs) or laboratory abnormalities until resolution or stabilisation. The primary endpoint was the percentage of patients with a viral load of < 50 HIV-1 RNA copies/ml at 24 weeks.

Efficacy analyses were carried out using the intention to treat time to loss of virologic response (ITT-TLOVR). In the primary analysis 11/12 (91.7%) and 10/12 (83.3%) patients achieved HIV-1 RNA < 50 copies/ml at weeks 24 and 48, respectively. At weeks 24 and 48, 12/12 (100%) and 11/12 (91.7%) had HIV-1 RNA < 400 copies/ml, respectively suggesting that virologic suppression was sustained[7,8]. The primary endpoints were supported by secondary endpoints. The mean $CD4^+$ cell count increased from 175 (19.5) x 10^6/l at week 24 to 221 (22.4) x 10^6/l at week 48[6–8].

The patients in this study had no significant differences in virologic responses when compared to treatment-naive HIV-1-infected adults[9] with no darunavir resistant associated mutations (DRV-RAMs) (see Table 1).

Table 1. Comparison of the DIONE and ARTEMIS study endpoints

	DIONE* (TMC114-C230) DRV/rtv	ARTEMIS† (TMC114-C211) DRV/rtv
Number of patients with data	12	343
Virologic parameters at week 24 and week 48		
Viral load < 50 copies/ml at week 24, n (%)	11 (91.7%)	273 (79.6%)
Viral load < 50 copies/ml at week 48, n (%)	10 (83.3%)	287 (83.7%)
Viral load < 400 copies/ml at week 24, n (%)	12 (100%)	315 (91.8%)
Viral load < 400 copies/ml at week 48, n (%)	11 (91.7%)	301 (87.8%)
Change from baseline in $\log_{10}$ viral load (copies/ml) at week 24, mean (SE) and median (range)	-3.03 (0.172) -3.23 (-3.8; -1.9)	-2.91 (0.054) -3.07 (-5.06; 0.08)
Change from baseline in $\log_{10}$ viral load (copies/ml) at week 48, mean (SE) and median (range)	-2.98 (0.182) -3.23 (-3.8; -1.9)	-2.77 (0.064) -3.04 (-5.06; 0.83)
Immunologic parameters		
Change from baseline in $CD4^+$ cell count (x 10^6 cells/l) at week 48, mean (SE) and median (range)	221 (22.4) 221 (64; 370)	154 (7.4) 137 (-182; 725)
*Conducted in patients aged 12 to < 18 years †Conducted in adult patients		

In the population pharmacokinetic analyses for the DIONE study, the DRV/rtv dose of 800 mg/100 mg once-daily given to adolescents appeared to be adequate, resulting in a geometric mean exposure of 77.8 microgram.h/ml; this represents 86.7% of the target

adult exposure (89.7microgram.h/ml). The median (range) pre-dose plasma concentration (C_{0h}) values in the adolescents and adult treatment-naive population were also comparable[1,6,10].

Treatment with DRV/rtv 800 mg/100 mg was safe and well tolerated in treatment-naive HIV-1-infected adolescents. There were no new safety findings to report compared with the known safety profile. Two patients reported more than one AE that was considered to be potentially related to treatment. However, these treatment-related AEs were grade 1 or 2 in severity. Three patients presented with grade 3 or 4 AEs but these were not considered to be due to treatment[1,6–8].

2.2 Treatment-experienced adolescents with no DRV-RAMs

Data to support the use of DRV/rtv in treatment-experienced adolescents aged 12 to 17 years and weighing more than 40 kg with no DRV-RAMs and who have plasma HIV-1 RNA < 100,000 copies/ml and $CD4^+$ cell count ≥ 100 cells x 10^6/l have been extrapolated from pharmacokinetic data on DRV/rtv in adult HIV-1 patients[1,11]. Exposure of adolescents to the once-daily DRV/rtv 800 mg/100 mg regimen produced pharmacokinetic/pharmacodynamic results that were comparable to those observed in the HIV-1-infected treatment-naive adults during the ARTEMIS study[1,7]. The DRV/rtv exposures and trough concentrations observed at steady-state in the population pharmacokinetic analyses in treatment-experienced adults with no DRV-RAMs (ODIN study) receiving DRV/rtv 800 mg/100 mg once-daily were similar to those observed in the population pharmacokinetic analyses for ARTEMIS study treatment-naive adults[11].

2.3 Points to note

- The company submission provided a comparison between DRV/rtv use in treatment-naive HIV-1-infected adolescents and use in treatment-naive HIV-1-infected adults and treatment-experienced HIV-1-infected patients with no DRV-RAMs[1]. In the guideline on the clinical development of medicinal products for the treatment of HIV infection, the Committee for Medicinal Products for Human Use (CHMP) stated that an extrapolation of efficacy data obtained in adults to children may be accepted providing there is reliable pharmacokinetic data in place to support the dosage recommendations[12]. Given the similarity of the disease in adults and children, CHMP acknowledged that there is no need to duplicate the evidence of efficacy obtained in adults, since the dose has been adequately selected on the basis of adult exposure[6].
- Although data obtained were supportive of DRV/rtv use, the DIONE study has some limitations including an open-label design and a small number of patients were recruited (n=12). CHMP stated, however, that the study design was adequate for an ART agent that has been shown to be efficacious in adults and that the results obtained are sufficient to support an extrapolation from adults to the adolescent population[6,12].
- The All Wales Medicines Strategy Group (AWMSG) has previously recommended the use of DRV/rtv tablets in treatment-naive[13], and treatment-experienced HIV-1-infected patients[14–16], and also the use of darunavir 100 mg/ml oral suspension in adults and treatment-experienced paediatric patients[17].
- Growth impairment and lipid abnormalities have been identified as potential risk factors associated with the long-term usage of DRV/rtv. An ongoing study will provide information on the potential risks associated with long-term treatment with DRV/rtv[6].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The applicant company estimates that there are six patients in Wales aged between 12 years and < 18 years who are eligible to receive DRV/rtv for this indication (one patient

who is treatment-naive and five patients who are treatment-experienced). It is assumed that the patient pool will remain constant over a period of time due to a relatively low incidence rate in Wales (0.005%)[1].

According to the company submission, treatment would cost £3,621 per patient per year for this indication. The company suggest that within the next five years, three patients will be treated with DRV/rtv. Therefore, the estimated five-year budget impact for darunavir ranges from £3,621 in year one to £10,863 in year five. The company calculate the five year total cost at £36,210. As, however, the treatment-experienced patients will be transferring from other ART-treatments, the company expect the net five year total cost to be lower than £36,210[1].

The company used data presented in the Collaborative HIV Paediatric Study (CHIPS)[18] to determine the number of patients eligible for DRV/rtv treatment in Wales. Of the 1,131 paediatric patients enrolled in the study, it was estimated that there were 14 patients HIV-1-infected in Wales and followed-up[18]; of these 14 patients, approximately seven (54%) patients were thought to be ≥ 12 years[1].

At the last follow up, it was estimated that 11% of patients in the CHIPS study aged ≥12 years remained ART-naive[1]. The company have applied this percentage to approximate that there is only one treatment-naive adolescent patient ≥ 12 years eligible for treatment in Wales, thus the remaining six patients are assumed to be treatment-experienced[1]. Of the six patients assumed to be treatment-experienced, the company have estimated that only one of these patients would have DRV-RAMs based on a UK paediatric study conducted between 1998 to 2008[18].

3.2. AWTTC critique of the budget impact analysis

- The majority of eligible patients are those who are treatment-experienced, but it is unclear in the submission as to which ART- treatments would be displaced by DRV/rtv[1].
- The number of paediatric patients ≥ 12 years of age in Wales who would be eligible for DRV/rtv treatment is based on estimates using data from the CHIPS study[18]. The number of children therefore who will be potentially eligible for treatment with darunavir is subject to a degree of uncertainty.
- In their submission, the company have included the cost of darunavir but have not taken into account the cost of ritonavir[1]. The company state this has not been included as all protease inhibitors must be prescribed with a similar dose of ritonavir booster.

3.3 Comparative unit costs

Table 2 provides comparative annual acquisition costs of darunavir 400 mg and 800 mg film-coated tablets and 100 mg/ml oral suspension and the comparators suggested by clinical experts were: lopinavir/ritonavir (Kaletra®) and efavirenz (Sustiva®).

Table 2. Examples of acquisition costs for darunavir and comparators for the treatment of HIV-1 infection in paediatric patients from the age of 12 years and at least 40 kg body weight.

Product	Example regimen	Cost per year*
darunavir (Prezista®) 100 mg/ml oral suspension	12 to < 18 years: - ART-naive adolescents: 800 mg once-daily (with 100 mg ritonavir) - ART-experienced adolescents with a body weight ≥ 40 kg and who have plasma HIV-1 RNA < 100,000 copies/ml and $CD4^+$ cell count ≥ 100 cells x 10^6/l: 800 mg once-daily (with 100 mg ritonavir)	£3,623 (+ £237 ritonavir)
darunavir (Prezista®) 400 mg and 800 mg film-coated tablets	12 to < 18 years: - ART-naive adolescents with a body weight ≥ 40 kg: 800 mg once-daily (with 100 mg ritonavir) - ART-experienced adolescents with a body weight ≥ 40 kg with no DRV-RAMs and who have plasma HIV-1 RNA < 100,000 copies/ml and $CD4^+$ cell count ≥ 100 cells x 10^6/l: 800 mg once-daily (with 100 mg ritonavir)	£3,623 (+ £237 ritonavir)
lopinavir/ritonavir (Kaletra®) 80mg/20 mg/ml oral suspension	12 to <18yrs 2.9 ml/m^2; max 5 ml twice daily	£3,740
lopinavir/ritonavir (Kaletra®) 200 mg/50 mg film-coated tablets	12 to < 18 years: -The recommended dose in adolescents: 2 x 200 mg lopinavir with 50 mg ritonavir twice daily	£3,472
efavirenz (Sustiva®) 30 mg/ml oral suspension	12 to < 18 years: - with a body weight ≥ 40 kg in combination with NRTIs with or without a PI: 24 ml once-daily	£2,620
efavirenz (Sustiva®) 600 mg film-coated tablets	- with a body weight ≥ 40 kg in combination with NRTIs with or without a PI: 600 mg once-daily	£2,437
* Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of 7 January 2014[19].		

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, darunavir (Prezista®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that darunavir (Prezista®) will be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 16 December 2013.
Date range of evidence search: No date limits were applied to database searches.

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Appendix: Previous AWMSG secretariat assessment report (published January 2011)

In January 2011 AWMSG appraised Darunavir (Prezista®) for the treatment of (human immunodeficiency virus (HIV-1) infection in antiretroviral treatment (ART)-experienced children and adolescents from the age of 6 years and at least 20 kg body weight) (AWTTC reference number 403). This advice is now incorporated into the Final Appraisal Recommendation (FAR) of Darunavir (Prezista®) for the treatment of (human immunodeficiency virus (HIV-1) infection in paediatric patients from the age of three years and at least 15 kg body weight. (AWTTC reference number 2579).

The original report for AWTTC reference number 403 is included below for completeness.

AWMSG Secretariat Assessment Report – Advice no. 0311

Darunavir (Prezista®▼) for the treatment of HIV-1 infection in treatment-experienced children and adolescents

This assessment report is based on evidence from a limited submission by Janssen-Cilag Limited submitted on 9 November 2010.

1.0 PRODUCT DETAILS

Licensed indication	Darunavir (Prezista®▼) co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in antiretroviral treatment (ART)-experienced children and adolescents from the age of 6 years and at least 20 kg body weight[1].
Dosing	Darunavir tablets should be taken with ritonavir twice daily in combination with food. The recommended dose of darunavir with low dose ritonavir for paediatric patients is based on body weight and should not exceed the recommended adult dose (600 mg darunavir plus 100 mg ritonavir, twice daily). Refer to the Summary of Product Characteristics (SPC) for further information regarding body weight-based dosing[1].
Marketing authorisation date	Date of first authorisation: 12 February 2007[1]. On 23 June 2009 an extension to the indication was granted to include the treatment of HIV-1 infection in ART-experienced adolescents and children of six years and above and with a body weight of more than 20 kg[2].
UK launch date	3 August 2009[3].

2.0 DECISION CONTEXT

2.1 Background

Since the advent of highly active antiretroviral therapy (HAART), HIV-1-infected children in Europe have become healthier and almost all are now surviving into adulthood[4]. The aim of treatment with antiretroviral drugs in children infected with HIV-1 is to achieve and sustain full viral load suppression whilst minimising short- and long-term drug toxicity[4]. In order to limit the risk of virological treatment failure, an objective of therapy is to suppress viral load to < 50 copies/ml[5]. For patients who experience sustained rebound in viral load, or who do not achieve viral load suppression after 24–36 weeks on their current treatment regimen, a change of therapy should be considered. The choice of new therapy should be guided by resistance testing to identify which drugs are active, that is to which resistance has not yet been acquired. In treatment-experienced patients, a new HIV-1 treatment should include at least two, and preferably three, active agents. If no or few therapy options exist, maintaining the existing failed regimen may simply allow further resistance mutations to accumulate whilst providing limited clinical benefit to the patient[5].

Darunavir is a protease inhibitor (PI) originally licensed in February 2007 for treatment of HIV-1 infection in highly pre-treated adults[1,6]. In November 2008 the indication for darunavir was extended to include moderately ART-experienced patients[2], and in January 2009 to include treatment-naïve patients at a recommended dose of 800 mg once daily (400 mg tablets only)[2,7]. In June 2009 the licence for darunavir was extended to include treatment of HIV-1 infection in ART-experienced adolescents and children aged six years and above with a body weight of more than 20 kg[2]. At this time, two new tablet formulations of 75 mg and 150 mg were made available to allow for appropriate dosing in children. Given the linear pharmacokinetics of darunavir, a biowaiver (a waiver of the requirement to demonstrate *in vivo* bioequivalence) was allowed by the European Medicines Agency (EMA) for these new tablet formulations[8].

Use of darunavir for the treatment of HIV-1 infection in treatment-experienced children and adolescents is the focus of this report. Existing All Wales Medicines Strategy Group (AWMSG) recommendations exist for use of darunavir in adults with HIV-1 infection (see section 2.3 for details).

2.2 Comparators

The Welsh Medicines Partnership (WMP) has identified tipranavir (Aptivus®▼) as the most appropriate comparator. As of September 2010, other PIs licensed for treatment of HIV-1 infections in children include:

- atazanavir (Reyataz®▼)[9]
- fosamprenavir (Telzir®)[10]
- lopinavir coformulated with ritonavir (Kaletra®)[11]
- nelfinavir (Viracept®)[12].

2.3 Guidance and related advice

- Paediatric European Network for Treatment of Aids (PENTA) guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection (2009)[4].
- Children's HIV Association standards of care for infants children and young people with HIV (2009)[13].
- British HIV Association (BHIVA) guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy (2008)[5].

AWMSG has previously issued recommendations for the use of darunavir in HIV-1-infected adults:

- Darunavir (Prezista®▼), co-administered with low dose ritonavir, is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in treatment-naïve patients[14].
- Darunavir (Prezista®▼) should be recommended within NHS Wales for the treatment of HIV-1 infection in highly pre-treated adults who have failed more than one regimen containing a PI, and where resistance profiling suggests it is appropriate. Use should be in accordance with BHIVA guidance[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

To evaluate the pharmacokinetics and efficacy of darunavir in the paediatric population, the company submission provided details of one open label, uncontrolled, phase II trial: TMC114-C212 (DELPHI)[16,17]. This study comprised two parts: part 1 focussed on darunavir dose selection in children; part 2 assessed the safety and efficacy of the selected dose of darunavir. Throughout the study, darunavir was administered twice daily in combination with ritonavir.

3.1 Part 1: dose selection

A total of 44 patients were randomised 1:1 to one of two body weight-adjusted doses of darunavir: either an adult-equivalent dose of darunavir (group A), or a dose 20–33% higher than the adult equivalent (group B)[16]. The duration of treatment was two weeks. Mean darunavir exposure was similar to adult exposure[18] for patients in group B, but slightly lower for those in group A[19]. The group B dose was therefore selected for use in part 2 of the study.

3.2 Part 2: main clinical study

Part 2 of the DELPHI study included 80 patients: all patients from part 1 and 36 newly recruited patients. All received darunavir at the dose selected in part 1, along with an optimised background antiretroviral treatment regimen[16]. The primary efficacy endpoint for part 2 was the number of patients with a confirmed virologic response (decrease in HIV-1 RNA of at least 1.0 $\log_{10}$ copies/ml) at week 24[16]; relevant secondary endpoints were the number of responders at all other time points[8]. Fifty-nine patients (74%) achieved the primary endpoint of a virologic response at week 24[16]. At week 48 (the last time point for which results are available), 52 patients (65%) had a confirmed virologic response. Response rates were highest at weeks 4 and 8: at both of these time points 82.5% of patients achieved a virologic response[8]. Although not listed as an endpoint, the number of patients with viral RNA levels < 50 copies/ml was also measured. At weeks 24 and 48, 40 patients (50%) and 38 patients (47.5%) respectively had HIV-1 RNA < 50 copies/ml[8]. The proportion of patients achieving a virologic response at weeks 24 and 48 was greatest in the youngest patients, and decreased with age; a similar pattern was observed for weight, with the highest response rates in the lowest weight band[8]. However, it should be noted that patient numbers for each subgroup were too small to allow any meaningful statistical comparison to be carried out.

Of the 80 patients treated in part 2, 24 (30%) experienced virologic failure (defined as a reduction in HIV-1 RNA of less than 1.0 $\log_{10}$ copies/ml)[16]. Seven patients never achieved virologic suppression; 17 patients were rebounders. Virologic response rates were lower (< 75% of overall response rates) for patients with at least three darunavir resistance-associated mutations at baseline, although it should be noted that the number of patients in this subgroup was small[16].

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

The paediatric safety population for darunavir consists of 77 HIV-1-infected patients aged 6–18 years treated for up to 48 weeks during the DELPHI study[8,16]. The Committee for Medicinal Products for Human Use (CHMP) note that this represents very limited safety information for this population, but concede that patient numbers are reasonable for this type of application and similar to those for other therapies in this class[8]. Adverse reactions observed in this population were similar to those observed in other studies of darunavir in the adult population; no new safety concerns were identified[1,8].

At the time of original marketing authorisation, CHMP noted that safety information for darunavir was limited, particularly with respect to head-to-head comparison of darunavir and other PIs[6]. Thus a condition of the marketing authorisation was to further characterise the safety profile of darunavir. Subsequent results submitted by the company to the EMA have indicated that the safety profile of darunavir is similar to that of lopinavir in treatment-experienced[20] patients. In treatment-naïve patients there is some evidence that the safety profile of darunavir is favourable to that of lopinavir[7], although it should be noted that darunavir is not licensed for use in treatment-naïve paediatric patients[1].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The study provided in the company submission provides efficacy evidence in a relatively small population of patients within the licensed dose and population. However, EMA guidance on the development of HIV medicines in the paediatric population does not require separate demonstration of efficacy in children, provided that reliable pharmacokinetic data support robust dose recommendations[21,22].
- In the EMA Assessment Report for this licence extension, CHMP comment that the measured virologic response at week 24 in the DELPHI study is comparable to the response seen in highly treatment-experienced adults. However, the Assessment Report also highlights that direct comparisons with the reported efficacy of other PIs in the paediatric population are not possible, due to heterogeneity between patient populations, and the uncontrolled, non-randomised design of most of these studies[8].
- The pivotal efficacy study (DELPHI) used an open-label design. Although it is recognised that double-blind study design is not always feasible in efficacy studies of HIV therapies[21], no rationale has been provided for the unblinded design of the DELPHI study.
- No evidence is available on the comparative efficacy or safety of darunavir with tipranavir, or indeed any other PI, in paediatric patients. The pivotal study for licensing of darunavir in treatment-experienced adults compared darunavir to a control group treated with optimised PI treatment, but did not include tipranavir in the control group[18].

- Patient ethnicities in the pivotal study DELPHI are notably different from those in Wales: 59% of patients in part 1 and 63% in part 2 were Caucasian[16]. Furthermore, the geographical location of the study centres, and therefore their relevance to Wales, is not clear from the company submission or any other source.
- According to EMA guidance, the preferred primary efficacy endpoint for studies of HIV medicines is the proportion of patients achieving and maintaining undetectable levels of HIV-1 RNA (< 50 copies/ml)[21]. This parameter was not a stated endpoint of the DELPHI study, although results are available and support the primary efficacy endpoint.
- Darunavir is not currently recommended for patients less than six years of age or those weighing < 20 kg, due to insufficient data in these groups[1].
- No licensed liquid preparation of darunavir is currently available; therapy may therefore be less suitable for children unable to swallow tablets.

6.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost-effectiveness evidence

The limited submission provided by the company does not include any evidence on the cost effectiveness of the use of darunavir (Prezista®▼) in patients aged six years and over[17]. Cost effectiveness evidence is not required for a limited submission.

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and methods

The company estimates there to be one patient with HIV-1 infection aged six years and over who will be eligible for treatment with darunavir in Wales. No details of how this estimate was arrived at, nor how patient numbers may change over time, have been provided by the company[17].

A simple costing exercise has been undertaken to list the annual costs of darunavir (dosed by body weight) and tipranavir (dosed by body surface area) for children with broadly comparable body weights and surface areas[17].

7.1.2 Results

On the assumption of one patient eligible for treatment, the company estimates the annual cost of darunavir in this population will range from £3,806 to £6,252 (inclusive of the cost of ritonavir, which must be given concomitantly) depending on patient body weight[17] (see Table 1).

Table 1. Company reported annual costs of darunavir and tipranavir[17].

Drug regimen	Patient weight or BSA	Twice daily dose	PI cost	Ritonavir cost	Total cost
Darunavir/ ritonavir	20 to < 30 kg	375/50 mg	£3,397	£409	£3,806
	30 to < 40 kg	450/60 mg	£4,076	£491	£4,567
	≥ 40 kg	600/100 mg	£5,435	£818	£6,252
Tipranavir/ ritonavir	0.93 m^2 (25 kg)	340/135 mg	£3,387	£1,104	£4,491
	1.18 m^2 (35 kg)	440/174 mg	£4,384	£1,423	£5,806
	1.41 m^2 (45 kg)	500/200 mg	£4,981	£1,635	£6,616

BSA = body surface area; PI = protease inhibitor.
Costs based on current BNF list prices[23].

7.1.3 WMP critique

Details are lacking regarding the methods and assumptions involved in estimating eligible patient numbers. The company has made effort to provide comparative annual costs for both darunavir and tipranavir in children aged six years and older, although it should be noted that their licensed indications differ with respect to the age, treatment history and resistance profiles of patients: darunavir is licensed for use in treatment-experienced children (aged six years and older) and adolescents[1]; tipranavir is licensed for use in highly pre-treated children from age 2 years with virus resistant to multiple protease inhibitors and no other treatment options[24,25]. It is therefore unlikely that the availability of darunavir will significantly impact on the use of tipranavir.

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that darunavir is not suitable for shared care within NHS Wales. Darunavir therapy should be initiated by a physician experienced in the management of HIV-1 infection[1].

8.2 Ongoing studies

- TMC114-TiDP29-C230 (ClinicalTrials.gov identifier NCT00915655) is a phase II, open-label, non-randomised trial of 800 mg darunavir in combination with 100 mg ritonavir in treatment-naïve HIV-1-infected patients aged 12 to 18 years. The primary outcome measure is the pharmacokinetic profile of this treatment over 24 weeks. Secondary outcomes include the safety, tolerability and efficacy of the treatment over 48 weeks. The estimated date for study completion is December 2010[26].
- TMC114-TiDP29-C228 (ClinicalTrials.gov identifier NCT00919854) is a phase II, open-label, non-randomised pharmacokinetic study of darunavir with ritonavir in treatment-experienced, HIV-1-infected children aged from three years to below six years. The primary outcome is the measured pharmacokinetic profile of darunavir in combination with ritonavir over 24 weeks. Secondary outcomes include resistance characteristics, safety, tolerability and efficacy of this treatment over 48 weeks. The estimated study completion date is January 2011[27].

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