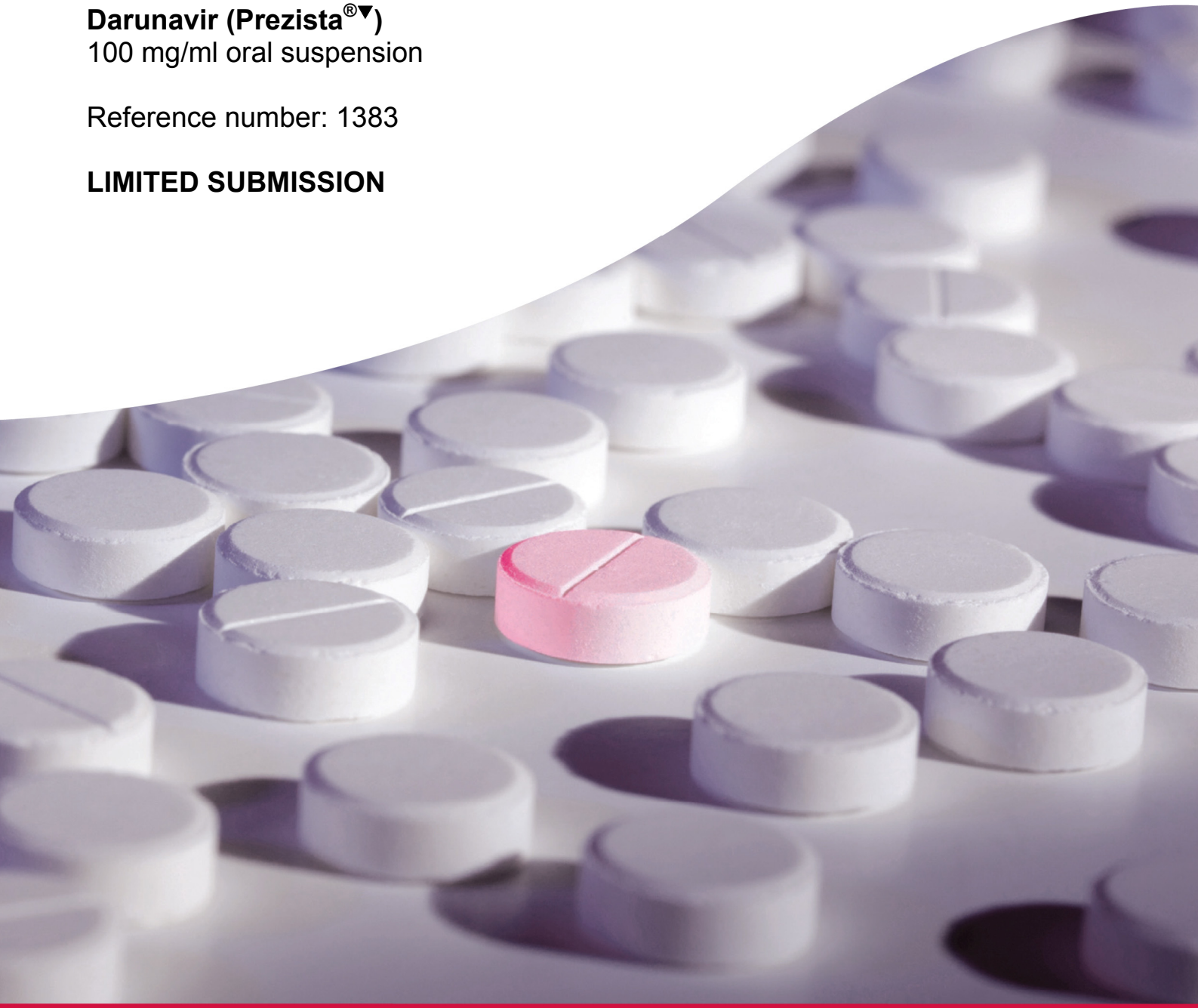
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Darunavir (Prezista®▼)
100 mg/ml oral suspension

Reference number: 1383

LIMITED SUBMISSION



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AWMSG Secretariat Assessment Report
Darunavir (Prezista®) 100 mg/ml oral suspension

This assessment report is based on evidence from a limited submission by Janssen-Cilag Ltd on 20 December 2012[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Darunavir (Prezista®) oral suspension, 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 adult patients, as well as antiretroviral therapy-experienced paediatric patients from the age of 3 years and at least 15 kg body weight. In deciding to initiate treatment with darunavir co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of darunavir[2].
Dosing	In children, recommended doses of darunavir oral suspension are: • 380 mg (3.8 ml) twice daily in children ≥ 15 kg to < 30 kg; • 460 mg (4.6 ml) twice daily in children ≥ 30 kg to < 40 kg; • 600 mg (6 ml) twice daily in children ≥ 40 kg. In adults, the recommended dose of darunavir oral suspension is 600 mg (6 ml) twice daily or 800 mg (8 ml) once daily, depending on previous treatment experience. Refer to the Summary of Product Characteristics (SPC) for further details[2].
Marketing authorisation date	Licence extension granted on 24 October 2012[1].
Comparators	The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were lopinavir/ritonavir (Kaletra®) oral solution and darunavir (Prezista®) film-coated tablets.
Limited submission details	Darunavir (Prezista®) oral suspension for the above indication met the following criteria for eligibility for a limited submission: • New formulation with a pro-rata or lower cost per treatment. • A minor licence extension.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The scope of this appraisal is the assessment of a new oral suspension formulation of darunavir. The introduction of this new formulation is accompanied by an extension to the licensed indication for darunavir, to include use in antiretroviral treatment-experienced paediatric patients aged at least 3 years (previously indicated for patients aged at least 6 years) and at least 15 kg body weight (previously at least 20 kg).

2.1 Clinical evidence supplied in the company submission

The company submission includes evidence on the clinical effectiveness of darunavir oral suspension in patients aged 3 to 6 years; bioavailability of darunavir oral

suspension and darunavir tablets; and comparative clinical effectiveness of darunavir and lopinavir.

2.1.1 Clinical effectiveness of darunavir oral suspension in children aged 3 to 6 years

To support the clinical effectiveness of darunavir oral suspension in children aged 3 to 6 years, the applicant company provided evidence from study TMC114-C228 (ARIEL). This was an open-label, phase II study with the aim of evaluating the pharmacokinetics, safety and antiviral activity of darunavir in children aged 3 to less than 6 years, weighing 10 to less than 20 kg. The study was conducted in Kenya and South Africa and enrolled 27 HIV treatment-experienced patients. Of these, 21 were included for analysis: the remaining six subjects were excluded due to issues with good clinical practice identified at their study site (see Section 2.2 for further details). The first two weeks of the trial were designed to support dose recommendations in the target population. All subjects received darunavir oral suspension twice daily (in combination with ritonavir and other antiretroviral therapies), initially at a dose of 20 mg/kg body weight. At the end of study week 2 this was reviewed based on pharmacokinetic results, and the dose adjusted to 25 mg/kg in patients weighing 10 kg to less than 15 kg, or a fixed dose of 375 mg in patients weighing 15 kg to less than 20 kg[1,3].

The primary efficacy parameter (number of patients with plasma viral load < 50 copies/ml) was met by 12 (57.1%) and 17 (81.0%) patients at study weeks 24 and 48 respectively. Adverse events reported were in line with the established safety profile for darunavir[1–3].

2.1.2 Bioavailability of darunavir oral suspension and darunavir tablets

Study TMC 114-C169 was an open-label, randomised crossover trial comparing the bioavailability of darunavir oral suspension to darunavir tablets in 17 healthy volunteers. Study participants received three 600 mg doses of darunavir (in combination with ritonavir), with a seven-day washout period between treatments: 2 × 300 mg tablets under fed conditions; 6 ml of 100 mg/ml oral suspension under fed conditions; and 6 ml of 100 mg/ml oral suspension under fasted conditions. Area under the curve and maximum plasma concentration were comparable between darunavir tablets and darunavir oral suspension (under both fasted and fed conditions)[1,3].

2.1.3 Comparative clinical effectiveness of darunavir and lopinavir

The company submission states that no evidence is available to directly compare the efficacy or safety of darunavir and lopinavir in children, and indirect comparison of studies of the individual medicines is not possible, due to heterogeneity between patient populations[1]. In the absence of this, evidence from two trials, both conducted in adults, comparing darunavir and lopinavir (TITAN and ARTEMIS) has been provided.

TITAN was an open-label, 96-week, phase III trial of darunavir versus lopinavir (both administered in combination with ritonavir) in early treatment-experienced HIV-1 infected adults who were naive to treatment with lopinavir[4,5]. Patients were randomised (n = 595) to darunavir/ritonavir 600 mg/100 mg tablets twice daily or lopinavir/ritonavir 400 mg/100 mg tablets twice daily; all patients also received an optimised background regimen. The primary outcome (patients with confirmed HIV-1 RNA level < 400 copies/ml at week 48) was met by 76.9% of darunavir-treated patients and 66.9% of lopinavir-treated patients; the predefined criterion for demonstrating noninferiority between treatments was met[5]. A similar pattern of results was reported after 96 weeks of treatment (HIV-1 RNA level < 400 copies/ml in 66.8% and 58.9% of patients in the darunavir and lopinavir groups respectively)[4].

ARTEMIS was an open-label, 192-week, phase III trial of darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1 infected adults. Patients were randomised (n = 689) to darunavir/ritonavir 800/100 mg tablets (once daily) or lopinavir/ritonavir

800/200 mg tablets (total daily dose, either once or twice daily); all patients received a tenofovir/emtricitabine-based background regimen. At week 192, the primary endpoint (patients with HIV-1 RNA < 50 copies/ml) was met by 68.8% of darunavir-treated patients and 57.2% of lopinavir-treated patients; the predefined criterion for demonstrating non-inferiority between treatments was met[6].

In both TITAN and ARTEMIS, adverse events were in line with the existing safety profiles for both darunavir and lopinavir[2,4,6,7].

2.2 Points to note

- The introduction of darunavir oral suspension increases the range of protease inhibitors available in a liquid formulation, potentially increasing the choice of antiretroviral therapies for patients who may require such a formulation (adults with swallowing difficulties or young children).
- The lack of a control group in the ARIEL study limits examination of the clinical effectiveness of darunavir oral suspension in children aged 3–6 years to naive unadjusted comparisons with studies of darunavir in older age groups (6 years and older)[8,9]. Nevertheless, European Medicines Agency guidelines on development of medicinal products for the treatment of HIV infection state that extrapolation of efficacy data obtained in adults to children may be acceptable for paediatric licence extensions[10].
- Six patients in the ARIEL study were excluded from the final analysis, following an inspection of the study site where these patients were enrolled and the identification of critical issues with good clinical practice at the site[3]. This further limited the already small sample size in this study.
- In the ARIEL study, 7 out of 21 patients reported that they did not like the taste of darunavir oral solution. The relationship between taste and adherence could not be established as adherence data were deemed unreliable[3].
- Patients included in the ARIEL study weighed between 12 and 20 kg. The licensed indication does not include patients weighing less than 15 kg, as the Committee for Medicinal Products for Human Use (CHMP) did not consider that darunavir (at the proposed dose of 20 mg/kg body weight) had been sufficiently evaluated in this patient group[3].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The budget impact analysis presented by the company[1] includes a comparison of the maximum annual costs associated with the use of darunavir oral suspension in combination with ritonavir, versus lopinavir/ritonavir (as Kaletra®) in eligible paediatric and adult HIV patients.

In children, the darunavir licence extension is for use as second line treatment in antiretroviral therapy (ART)-experienced patients aged from 3 to 6 years and weighing ≥ 15kg. The company estimates that there are currently two paediatric patients eligible for treatment with darunavir oral suspension in Wales, based on data from University Hospital Wales, Cardiff, reported in a cohort study[11]. As the dosing of darunavir is dependent on body weight, the company estimates that the total annual cost for the two patients would range between £7,702 and £12,505, compared with costs ranging between £1,613 and £3,763 for Kaletra® (dosed based on body surface area). Hence, the company estimates that using darunavir would result in a net cost of between £3,226 and £7,527 per year for two paediatric patients. Compared with darunavir film-coated tablets, the use of darunavir oral suspension is estimated to have a budget impact of £45 and £90 per year, in patients with body weights of 15–30 kg and 30–40 kg, respectively.

Based on a reported prevalence of swallowing difficulties in HIV patients treated at University Hospital Wales, Cardiff, of 1.3%, the company estimates that there are 20 adult HIV patients with swallowing difficulties in Wales for whom darunavir oral suspension could be used. It is assumed that these patients would be currently treated with Kaletra® oral solution. The use of darunavir oral suspension in these patients is estimated to increase annual cost by either £269 or £2,490 per patient, depending on the dose of darunavir required (800 mg/100mg once daily or 600 mg/100mg twice daily, respectively).

3.2 AWTTC critique of the budget impact analysis

- The estimated number of eligible patients is based on data from one centre in South Wales. Hence, patients from North Wales, who are treated at centres in England, are not included in this estimate. The company's budget impact analysis is provided only for the first year of uptake, rather than over a five year period, which implicitly assumes these figures remain static over time.
- It is assumed that darunavir oral suspension is interchangeable with Kaletra® oral solution; this may not be the case in practice due to differences in the factors taken into account when deciding to initiate treatment (e.g. licensed indications individual patient profiles and treatment history).

3.3 Table of comparative unit costs

Table 1 provides comparative annual acquisition costs of darunavir oral suspension and the comparators requested by AWTTC: darunavir film-coated tablets and Kaletra® oral solution.

Table 1. Example comparative annual drug acquisition costs for darunavir oral suspension and its comparators

Product	Example regimen	Cost per year
Prezista® (darunavir) Oral suspension 100 mg/ml	Paediatrics: 15–30 kg: 375 mg twice daily (with 50 mg ritonavir) 30–40 kg :450 mg twice daily (with 60 mg ritonavir) ≥ 40 kg: 600 mg twice daily (with 100 mg ritonavir)	£3,442 (+£409 ritonavir) to £5,435 (+ £818 ritonavir)
	Adults: - ART-naive adults and a subgroup of ART-experienced adults (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 × 10^6/l): 800 mg once daily (with 100 mg ritonavir) - ART-experienced adults, including those that have been highly pre-treated: 600 mg twice daily (with 100 mg ritonavir)	£3,623 (+ £409 ritonavir) to £5,435 (+ £818 for ritonavir)
Prezista® (darunavir) Oral, film coated tablets 75 mg, 150 mg, 400 mg and 600 mg	Paediatrics: 15–30 kg: 375 mg twice daily 30–40 kg :450 mg twice daily ≥ 40 kg: 600 mg twice daily	£3,397 (+ £409 ritonavir) to £5,435 (+ £818 for ritonavir)
	Adults: - ART-naive adults and a subgroup of ART-experienced adults (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 × 10^6/l): 800 mg once daily (with 100 mg ritonavir) - ART-experienced adults, including those that have been highly pre-treated: 600 mg twice daily (with 100 mg ritonavir)	£3,623 (+ £409 ritonavir) to £5,435 (+ £818 for ritonavir)
Kaletra® (lopinavir/ritonavir) Oral solution 80 mg lopinavir + 20 mg ritonavir/ml	Under 2 years, not recommended. Over 2 years, according to body surface area: 2.9 ml/m^2 twice daily	£1,627 to £3,688*

**Calculated based on body surface area of 0.75 m^2 and 1.7 m^2 (corresponding to a weight ≥ 15 kg and ≥ 45 kg, respectively)*
Refer to the relevant SPCs[2,7] for full dosing details.
Costs of comparators are based on MIMS[12] list prices as of 31 January 2013.
This table does not imply therapeutic equivalence of drugs or the stated doses.

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, darunavir oral suspension is appropriate for specialist only prescribing within NHS Wales for the stated indication.

4.2 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).

4.3 Evidence search

Date of evidence search: 29 January 2013.
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Janssen-Cilag Ltd. Form C. Limited appraisal submission. Darunavir (Prezista®) oral suspension. Dec 2012.

2 Janssen-Cilag Ltd. Prezista® 75 mg, 150 mg, 400 mg, 600 mg 800 mg film-coated tablets and oral suspension 100 mg/ml. Summary of Product Characteristics. Jan 2013. Available at: http://www.medicines.org.uk/EMC/medicine/27325. Accessed Jan 2013.

3 Committee for Medicinal Products for Human Use. Assessment report: Prezista. Procedure No.: EMEA/H/C/000707/X/0041/G. Jul 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000707/WC500134741.pdf. Accessed Jan 2013.

4 Banhegyi D, Katlama C, da Cunha CA et al. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. *Curr HIV Res* 2012; 10 (2): 171-81.

5 Valdez Madruga J, Berger D, McMurchie M et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. *Lancet* 2007; 370: 49-58.

6 Orkin C, DeJesus E, Khanlou H et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. *HIV Med* 2013; 14 (1): 49-59.

7 Abbvie Ltd. Kaletra® 100 mg/25 mg film-coated tablets. Summary of product characteristics. Nov 2012. Available at: http://www.medicines.org.uk/emc/medicine/20855. Accessed Jan 2013.

8 Arasteh K, Yeni P, Pozniak A et al. Efficacy and safety of darunavir/ritonavir in treatment-experienced HIV type-1 patients in the POWER 1, 2 and 3 trials at week 96. *Antivir Ther* 2009; 14 (6): 859-64.

9 Blanche S, Bologna R, Cahn P et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS* 2009; 23 (15): 2005-13.

10 European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of HIV infection. Nov 2008. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003460.pdf. Accessed Jan 2013.

11 Collaborative HIV Paediatric Study (CHIPS). Cohort summary data. Mar 2012. Available at: http://www.chipscohort.ac.uk/summary_data.asp. Accessed Jan 2013.

12 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Dec 2012. Available at: http://www.mims.co.uk/. Accessed Jan 2013.