AWMSG Secretariat Assessment Report – Advice no. 1810
Atazanavir (Reyataz®▼) for the treatment of HIV-1 infected paediatric patients in combination with other antiretroviral medicinal products

1.0 PRODUCT DETAILS

Licensed indication	Atazanavir (Reyataz®▼) co-administered with low dose ritonavir for the treatment of HIV-1 infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products. Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). There are very limited data available from children aged 6 to 18 years. The choice of atazanavir in treatment-experienced adult and paediatric patients should be based on individual viral resistance testing and the patient's treatment history[1].
Dosing	The dose of atazanavir capsules for paediatric patients is based on body weight and should not exceed the recommended adult dose. Refer to the summary of product characteristics (SPC) for further details. Atazanavir capsules must be taken with ritonavir and with food[1].
Marketing authorisation date	7 July 2010[2].
UK launch date	7 July 2010[2].

2.0 DECISION CONTEXT

2.1 Background

HIV-related infections and mortality have significantly decreased since the introduction of highly active antiretroviral therapies (HAART) to treat HIV-1 infections[3]. In order to achieve maximum potency, durability, adherence and tolerability, and to avoid long-term toxicities and any likely drug interaction, HAART regimens must be individualised for patients with HIV-1[4]. In general, a HAART regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs), in addition to a non-nucleoside reverse transcriptase inhibitor (NNRTI), is the preferred first line regimen in newly diagnosed HIV-1 patients in whom treatment is recommended. In patients who experience first virological failure on this type of regimen, it is generally recommended that the regimen is switched to one including two different NRTIs, plus a protease inhibitor (PI) taken with ritonavir as a 'booster' of PI pharmacokinetics. First line use of boosted PIs is usually reserved for specific groups of patients, such as those with primary NRTI and/or NNRTI resistance, women who wish to become pregnant, and those with psychiatric problems[4].

Atazanavir was originally licensed for treatment-experienced adult patients in March 2004[1]. The licence was extended in June 2008 to include treatment-naive adults, and in July 2010 to include both treatment-experienced and treatment-naïve paediatric patients[5]. Use of atazanavir in adults has previously been assessed by the All Wales Medicines Strategy Group (AWMSG) (see section 2.3). The assessment presented here concerns only the use of atazanavir for paediatric patients. According to the European Medicines Agency (EMA), granting of this licence extension does not require the duplication of clinical efficacy and safety evidence already obtained in adults[6]; the clinical development of this class of therapy in children should focus on dose selection[3].

2.2 Comparators

The agreed comparator is lopinavir coformulated with ritonavir (Kaletra®). As of September 2010, other PIs licensed for treatment of HIV-1 infections in children include:

- fosamprenavir (Telzir®) for use in treatment-naïve or treatment-experienced patients[7];
- darunavir (Prezista®▼) for use in treatment-experienced patients only[8];
- tipranavir (Aptivus®▼) capsules for highly pretreated patients aged 12 years and over only[9].

2.3 Guidance and related advice

- Paediatric European Network for Treatment of Aids 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection[10].
- British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy, 2008[4].

AWMSG has previously issued recommendations for the use of atazanavir and other PIs in adults with HIV-1 infections:

- Atazanavir is recommended as an option for treatment of HIV-1 infected adults, both treatment-experienced[11] and treatment-naïve[12].
- Tipranavir is recommended for treatment of HIV-1 infection only in highly pretreated adults who have failed multiple PIs and where resistance profiling suggests it use is appropriate[13].
- Darunavir is recommended as an option for treatment of HIV-1 infection in treatment-naïve adults[14], and in highly pretreated adults who have failed more than one PI-containing regimen (where resistance profiling suggests it use is appropriate)[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submitted details of a single atazanavir study in support of their application[2]. Study PACTG 1020-A is a multicentre, open-label, phase I/II study in HIV-infected treatment-naïve and treatment-experienced patients aged 91 days to 21 years[3]. The study has a planned duration of 96 weeks; results are available only from the interim datalock at 48 weeks[2,3].

A total of 182 patients received atazanavir (in powder or capsule form and either with or without ritonavir) in combination with two NRTIs. Atazanavir is licensed only in capsule form and in combination with ritonavir[1]. Therefore, the efficacy results considered as part of this assessment are restricted to patients receiving this form of treatment, and who were within the age group stated in the licensed indication (6–18 years). This subgroup comprised 41 patients (16 treatment-naïve, 25 treatment-experienced)[1].

The primary objectives of the study were to determine the pharmacokinetic profile, dosing schedule, safety and tolerability of atazanavir within the stated dosing regimens and formulations[3]. Although the study was not primarily intended to assess efficacy of atazanavir, a relevant secondary objective was to measure antiretroviral activity in terms of viral load and CD4 cell count. Outcomes are detailed in table 1.

Table 1. Efficacy outcomes at week 48 in patients aged 6–18 years in study PACTG 1020-A[1,2].

Parameter	Treatment-naive atazanavir capsules/ritonavir (300 mg/100 mg once daily) n = 16	Treatment-experienced atazanavir capsules/ritonavir (300 mg/100 mg once daily) n = 25
HIV RNA < 50 copies/ml, %		
All patients	81 (13/16)	24 (6/25)
HIV RNA < 400 copies/ml, %		
All patients	88 (14/16)	32 (8/25)
CD4 mean change from baseline†, cells/mm^3		
All patients	293 (n = 14*)	229 (n = 14*)

*Number of patients evaluable. †Mean baseline CD4 cell count in treatment-naïve patients: 344 cells/mm^3 (range: 2–800 cells/mm^3). Mean baseline CD4 cell count in treatment-experienced patients: 522 cells/mm^3 (range: 100–1157 cells/mm^3).

Assessment of the development of virological resistance is listed as a secondary objective of study PACTG 1020-A in the Committee for Medicinal Products for Human Use (CHMP) variation assessment report[3]. However, it should be noted that this objective is not listed in the study details registered at ClinicalTrials.gov[16]; it is therefore unclear whether this was an original objective of the study design. For all treatment-naïve patients dosed with atazanavir and ritonavir, 9 out of 50 had baseline genotypic resistance, whilst newly emergent genotypic resistance profiles were observed for 7 out of 50. For all treatment-experienced patients dosed with atazanavir and ritonavir, 30 out of 47 had baseline genotypic resistance, whilst newly emergent genotypic resistance profiles were observed for 21 out of 47 (ref. 3). No resistance profiles are available specific to the subgroup of 41 patients treated according to the licensed indication for atazanavir. Efficacy results are available for 18 treatment-experienced patients treated with atazanavir and ritonavir, stratified by PI mutation profile: 27% (4 out of 15) of patients with 0–2 PI mutations had HIV RNA < 50 copies/ml. No patients (0 of 3) with ≥ 4 PI mutations had HIV RNA < 50 copies/ml. No results are available for patients with 3 PI mutations[1,2].

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

Safety data is derived from the total study population in PACTG 1020-A. Overall the safety profile in children was comparable to that observed in adults[1,3], although the rate of discontinuation due to adverse events was more frequent than the equivalent rate in adult studies[3]. Another area of concern is the increased incidence of atrioventricular block and prolongations in PR interval in children compared to adults; this effect was dose-dependent. This issue is highlighted by the updated SPC[1], and will be monitored by the proposed pharmacovigilance[3]. Pharmacokinetic data from PACTG 1020-A found that peak-to-trough ratios and mean C_{max} values were higher in children than in adults[3]. This effect was most pronounced in the youngest children (6 years and under).

This could contribute to the increased rate of adverse events in the paediatric population. In light of this, the indication was revised by the EMA to exclude patients < 6 years of age[3].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- Clinical efficacy data for atazanavir in the paediatric population is limited to a single phase I/II study. In this study, only a subgroup of patients was dosed within the licensed indication for atazanavir, and no active comparator was included. Nevertheless, the EMA are of the opinion that extrapolation of efficacy data from adults is acceptable[3,6]. In adults, antiviral efficacy of atazanavir has been shown to be non-inferior to lopinavir for up to 48 weeks of treatment[1].
- Although safety data is available for 182 patients from study PACTG-1020-A, only a limited number of these patients were treated with atazanavir according to the extended indication (16 treatment-naïve and 25 treatment-experienced patients). Therefore, post-marketing surveillance will be key to monitoring safety in the licensed population[3].
- In terms of antiviral efficacy, results in children do not compare favourably to equivalent studies in adults. After 48 weeks of therapy, 66% of treatment-naïve paediatric patients had HIV RNA < 50 copies/ml, compared with 78% of adults. At the same time point 26% of treatment-experienced paediatric patients had HIV RNA < 50 copies/ml, compared with 36% of adults[3].
- In common with the adult population, atazanavir is considerably more effective in treatment-naïve than treatment-experienced paediatric patients. However, in contrast to treatment-experienced adult patients, the number of PI mutations above which atazanavir is predicted to be ineffective has not been determined in the licensed paediatric population[1,3]. The SPC states that whilst in adults no benefit can be expected in patients with ≥ 4 PI mutations, available data suggest that atazanavir in combination with ritonavir may not be effective in treatment-experienced children even with very few (< 3) mutations[1].
- Atazanavir can be taken at the same time as ritonavir as a once daily dose in adults and in paediatric patients[1]. With respect to patient adherence this offers an advantage over lopinavir, for which the standard recommended dosing is twice daily[17].
- In paediatric patients, the recommended lopinavir dose is based on body surface area[17]. Atazanavir is dosed based on body weight[1], making dosing calculations simpler in clinical practice.
- None of the evidence submitted for the use of atazanavir in paediatric patients is from studies conducted in the European Union: study PACTG 1020-A was conducted in South Africa and the United States. Patient demographics may therefore vary considerably from Wales.

6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost effectiveness evidence

The abbreviated company submission[2] does not include any evidence on the cost-effectiveness of the use of atazanavir in paediatric patients aged 6–18 years.

6.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of atazanavir in the paediatric patient population.

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and Methods

The budget impact analysis explores the displacement of lopinavir/ritonavir by atazanavir over a three year period. The company reports that there were 15 paediatric HIV patients aged 6–18 years in Wales in 2008[2], based on data obtained directly from the Health Protection Agency. Patient numbers are assumed to remain constant throughout the three year time horizon.

The company has assumed that patients are distributed equally among the body weight and body surface area categories used to determine the daily dose of atazanavir (plus ritonavir) and lopinavir/ritonavir. In the absence of market share data in the paediatric patient population, the company has estimated that lopinavir/ritonavir is used in 20% of patients (equivalent to three patients per year). Atazanavir is assumed to displace lopinavir/ritonavir in 10% of patients in year 1, 20% in year 2 and 30% in year 3.

7.1.2 Results

The company-estimated budget impact is summarised in table 2.

Table 2. Company estimates of budget impact[2].

	Number of patients on lopinavir/ ritonavir	Total annual cost of lopinavir/ ritonavir	Number of patients on atazanavir†	Total annual cost of atazanavir + ritonavir	Total cost (lopinavir + atazanavir)*
Currently	3	£8,415	0	£0	**£8,415**
Year 1	3	£8,415	0 (0.3)	£0	**£8,415**
Year 2	2	£5,610	1 (0.6)	£2,870	**£8,480**
Year 3	2	£5,610	1 (0.9)	£2,870	**£8,480**

*Includes ritonavir components. See discussion in section 7.1.3. †Figures are rounded to the nearest integer; parentheses are the true calculated figure.

7.1.3 WMP critique of the company's budget impact estimates

Due to a reported lack of epidemiological data in the target population, the number of patients expected to be eligible for treatment with atazanavir, and the uptake of atazanavir, are subject to uncertainty. Dosing for lopinavir/ritonavir and atazanavir (plus ritonavir), and hence costs, are based on patient body surface area or weight categories. The company has pragmatically estimated costs based on the assumption of an equal distribution across these dosing categories. However, as reported eligible patient numbers are small, the actual annual costs for treating all eligible patients may differ from those reported by the company, depending on actual patient characteristics (see table 3 for range of actual costs).

7.2 Comparative unit costs

Table 3 provides example treatment regimens with atazanavir (plus ritonavir) and lopinavir/ritonavir, which are licensed for use in treatment-naive and treatment-experienced patients[1,17]. Other PIs licensed for use in children include darunavir (Prezista®▼, children aged 6 years and older)[8] and tipranavir (Aptivus®▼, children aged 12 years and older)[9], both of which are limited to use in treatment-experienced patients. Treatment must be tailored to the individual patient.

Table 3. Example annual costs of atazanavir and lopinavir.

Drug	Example daily regimen	Annual cost[18]
Atazanavir (Reyataz®▼) plus 100 mg ritonavir (Norvir®) once daily	Body weight 15 to < 20kg: 150 mg once daily	£1846 + £409 = £2255
	Body weight 20 to < 40kg: 200 mg once daily	£1846 + £409 = £2255
	Body weight ≥ 40kg: 300 mg once daily	£3690 + £409 = £4099
Lopinavir/ritonavir (Kaletra®)	Body surface area 0.5 to < 0.9 m^2: 2 × 100/25 mg twice daily	£1870
	Body surface area 0.9 to < 1.4 m^2: 3 × 100/25 mg twice daily	£2805
	Body surface area ≥ 1.4 m^2: 2 × 100/25 mg twice daily	£3740
This table does not imply therapeutic equivalence of the drugs or doses. See the individual SPCs[1,17] and BNF for recommendations. All costs calculated from BNF list prices[3]		

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that atazanavir is not suitable for shared care within NHS Wales. Atazanavir should be initiated by a physician experienced in the management of HIV infection.

8.2 Ongoing studies

Study PCH 09-004 is a phase IV non-randomised open-label trial in HIV-1 infected children (aged 6–18 years) with high cholesterol or high triglycerides as a result of antiretroviral treatment[19]. The objective of this study is to determine whether switching from a pre-existing PI or NNRTI-containing regimen to boosted atazanavir can maintain antiviral efficacy whilst reducing patient cholesterol and triglyceride levels and increasing patient satisfaction and adherence. The estimated primary completion date for this study was April 2010[19], but as of October 2010 no results are available.

This assessment report is based on evidence from a limited submission by Bristol Myers Squibb Pharmaceutical Ltd on 16 August 2010.

This report should be cited as:
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REFERENCES

1 Bristol-Myers Squibb Pharmaceuticals Ltd. Reyataz®▼ 150 mg, 200 mg and 300 mg hard capsules. Summary of product characteristics. Jul 2010. Available at: http://www.medicines.org.uk/emc/medicine/14145. Accessed Sep 2010.

2 Bristol-Myers Squibb Pharmaceuticals Ltd. Form C. AWMSG limited submission. Reyataz®▼. Aug 2010.

3 European Medicines Agency. CHMP variation assessment report. Reyataz®▼. Apr 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000494/WC500094745.pdf.

4 Gazzard BG on behalf of the BHIVA Treatment Guidelines Writing Group. British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Medicine* 2010; 9: 563-608.

5 European Medicines Agency. Reyataz®▼. Procedural steps taken and scientific information after the authorisation. Aug 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000494/WC500056383.pdf. Accessed Sep 2010.

6 European Medicines Agency. Report on the meeting of the Paediatric Human Immunodeficiency Virus Expert Group. May 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/05/WC500090228.pdf.

7 ViiV Healthcare UK Ltd. Telzir 700 mg film-coated tablets. Summary of product characteristics. Apr 2010. Available at: http://www.medicines.org.uk/EMC/medicine/14819. Accessed Sep 2010.

8 Janssen-Cilag Ltd. Prezista 75 mg, 150 mg, 400 mg, 600 mg film-coated tablets. Jul 2010. Available at: http://www.medicines.org.uk/EMC/medicine/22152. Accessed Sep 2010.

9 Boehringer Ingelheim Limited. Aptivus 250 mg soft capsules. Summary of product characteristics. Nov 2009. Available at: http://www.medicines.org.uk/EMC/medicine/17027. Accessed Sep 2010.

10 PENTA steering committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Medicine* 2009; 10: 591-613.

11 All Wales Medicines Strategy Group. Final Appraisal Report: Atazanavir (Reyataz®▼) for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-experienced patients. 2008. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Atazanavir%20_Reyataz_%20Experienced%20FAR.pdf.

12 All Wales Medicines Strategy Group. Final Appraisal Report: Atazanavir (Reyataz®q) for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-naive patients. Dec 2008. Available at: http://www.wales.nhs.uk/sites3/Documents/371/atazanavir%20_Reyataz_%20Naive%20FAR.pdf.

13 All Wales Medicines Strategy Group. Final appraisal report: Tipranavir. 2007. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Tipranavir%20%28Aptivus%29%20FARfinal.pdf.

14 All Wales Medicines Strategy Group. Final appraisal report. Darunavir (Prezista®q) for the treatment of HIV-1 infected, treatment-naïve adults in combination with other antiretroviral medicinal products. Dec 2009. Available at: http://www.wales.nhs.uk/sites3/Documents/371/darunavir%5FPrezista%5F%20FAR.pdf.

15 All Wales Medicines Strategy Group. Final appraisal report: Darunavir. Aug 2007. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Darunavir%28Prezista%29%20FAR%20final.pdf.
16 ClinicalTrials.gov. NCT00006604. Atazanavir used in combination with other anti-HIV drugs in HIV infected infants, children, and adolescents. Aug 2010. Available at: http://clinicaltrials.gov/ct2/show/NCT00006604. Accessed Sep 2010.
17 Abbott Laboratories Limited. Kaletra® 200 mg/50 mg film-coated tablets. Summary of product characteristics. Aug 2010. Available at: http://www.medicines.org.uk/emc/medicine/18442. Accessed Sep 2010.
18 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary No. 59.* Mar 2010.
19 ClinicalTrials.gov. NCT00940771. Equivalence of boosted atazanavir-based regimens and currently effective HAART regimens. Jan 2010. Available at: http://clinicaltrials.gov/ct2/show/NCT00940771. Accessed Sep 2010.