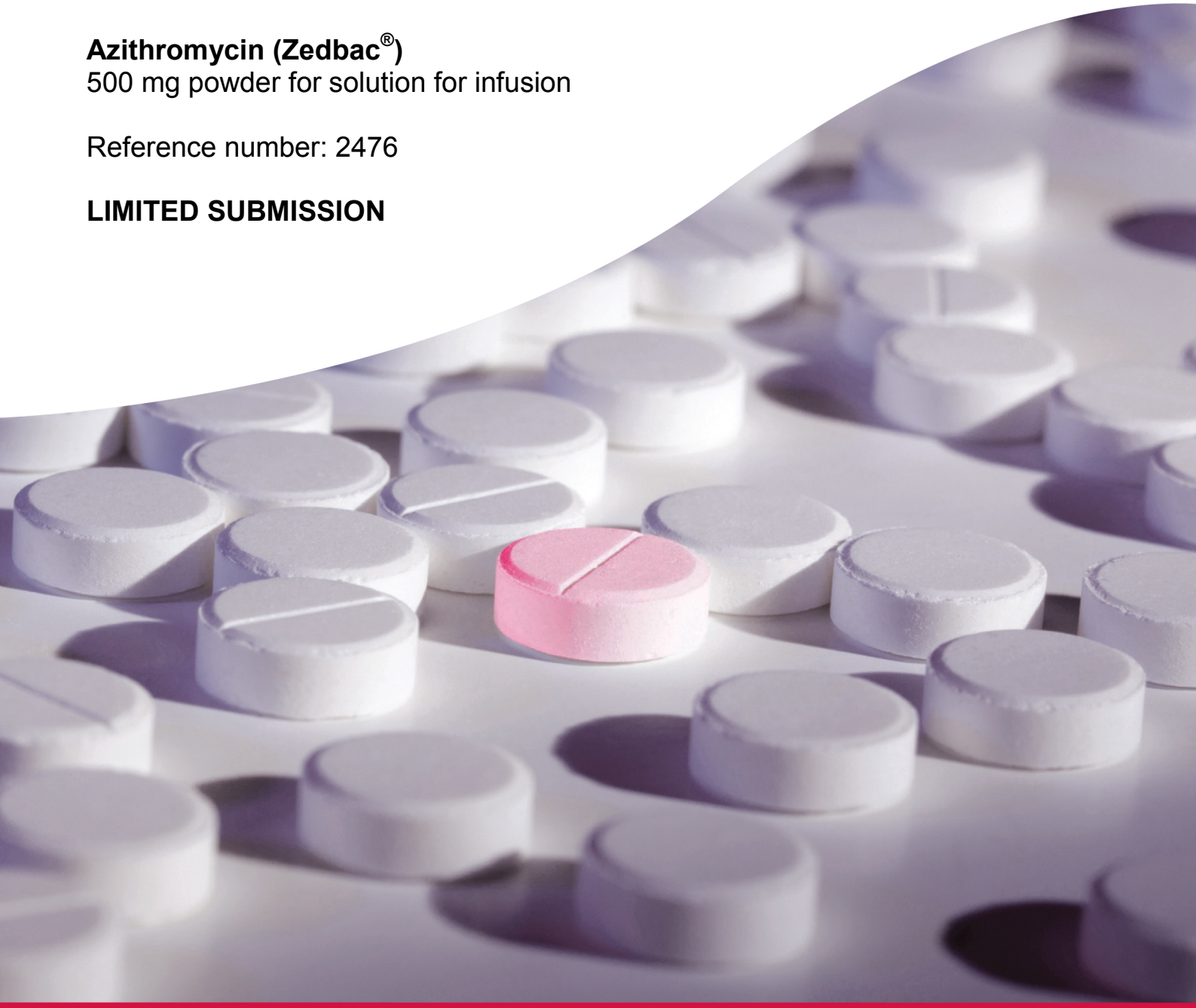
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Azithromycin (Zedbac®)
500 mg powder for solution for infusion

Reference number: 2476

LIMITED SUBMISSION



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AWMSG Secretariat Assessment Report
Azithromycin (Zedbac®) 500 mg powder for solution for infusion

This assessment report is based on evidence from a limited submission by Aspire Pharma Ltd on 28 March 2014[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Azithromycin (Zedbac®) as powder for solution for infusion is indicated for the treatment of the following infections: • community-acquired pneumonia (CAP) due to susceptible microorganisms, in adult patients where initial intravenous therapy is required. • pelvic inflammatory disease (PID) due to susceptible microorganisms, in patients where initial intravenous therapy is required. Consideration should be given to official guidance regarding the appropriate use of antibacterial agents[2].
Dosing	The recommended dose of azithromycin (as powder for solution for infusion) for the treatment of adult patients with community-acquired pneumonia is 500 mg administered as a single intravenous daily dose for at least two consecutive days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 500 mg for up to 7 to 10 days of treatment. Transition to oral therapy should be carried out when indicated by the doctor and according to the clinical response. The recommended dose of azithromycin (azithromycin as powder for solution for infusion) for the treatment of adult patients with pelvic inflammatory disease is 500 mg administered as a single intravenous daily dose for one or two days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 250 mg up to 7 days of treatment. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	19 September 2012[2]
UK launch date	02 October 2013[1]
Comparators	The comparator included in the company submission was clarithromycin IV (Klaricid®)[1].
Limited submission details	Azithromycin (Zedbac®) for the above indication met the following criteria for eligibility for a limited submission: • Significant new formulation with a pro-rata or lower cost per treatment. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparator.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The All Wales Medicines Strategy Group (AWMSG) appraises a medicine within the whole of its licensed indication. However, the applicant company has requested that AWMSG considers azithromycin as an alternative intravenous (IV) treatment option for community-acquired pneumonia (CAP) only and has not provided data for use in pelvic inflammatory disease (PID).

The licence for azithromycin IV (Zedbac®) was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) based on generic marketing authorisation for the Portuguese reference product Zithromax® IV, which is not licensed in the UK as of May 2014. The applicant company conducted a literature search and provided data relating to the reference product to inform their submission[1].

The most relevant evidence is provided by a study conducted by Tamm et al (2007)[3], and is summarised in Section 2.1. A supporting study[4] is briefly described in Section 2.1.1. In addition, a number of other studies were highlighted in the submission as evidence for the use of azithromycin; however, these will not be discussed further as they do not evaluate the IV preparation which is the focus of this appraisal[1,5–8]. Two further studies, one comparing levofloxacin to ceftriaxone plus azithromycin IV and the other comparing levofloxacin to ceftriaxone plus clarithromycin were also included in the submission; however, no indirect comparison analysis could be provided[1,9,10]. The company state that study designs and endpoints were too diverse to be able to successfully provide robust comparative data and as such, these studies will not be discussed further.

The British Thoracic Society (BTS) guidelines for the management of CAP in adults recommend the use of combination antibiotic therapy in the treatment of hospitalised patients with moderate to severe CAP[11]. In their submission, the company also included information on studies which evaluated azithromycin IV as monotherapy for the treatment of CAP. These were considered to be broadly supportive in demonstrating the efficacy and safety of azithromycin[4,12–14], and therefore, the reported cure or failure rates at end of study (EOS) from these studies are summarised in Appendix 1.

2.1 Tamm et al (2007)[3]

This study was a multicentre, prospective, randomised, open-label trial, which compared the efficacy and safety of azithromycin IV to clarithromycin IV or erythromycin IV in combination therapy for the treatment of patients diagnosed with CAP requiring hospitalisation[3]. Patients (n = 278) were randomised to two groups: ceftriaxone IV plus azithromycin IV followed by step-down oral azithromycin daily (n = 135), or ceftriaxone IV plus clarithromycin IV or erythromycin IV followed by step-down oral clarithromycin or erythromycin (n = 143)[3].

The primary efficacy endpoint was the clinical response at the EOS for the clinically evaluable population. Clinical response was based on the investigator's assessment of radiological findings and clinical signs and symptoms at baseline compared to EOS and classified as 'cure' or 'failure'. The clinical success rates for the evaluable population at EOS were similar: 78.6% for the ceftriaxone plus azithromycin IV group and 78.4% for the ceftriaxone plus clarithromycin IV or erythromycin IV group. Secondary endpoints were found to be consistent with the primary efficacy endpoint[3].

Treatment-related adverse events were 32.6% in the ceftriaxone plus azithromycin IV group compared to 40.6% in the ceftriaxone plus clarithromycin or erythromycin IV group. Infusion-related events (infection/inflammation) were significantly lower in the ceftriaxone plus azithromycin IV group versus the ceftriaxone plus clarithromycin or erythromycin IV group (14.1% versus 23.8%, p = 0.04)[3].

Tamm et al concluded that the study demonstrated equivalent efficacy and safety of ceftriaxone plus azithromycin to the comparator regimen in the treatment of hospitalised patients with CAP[3].

2.1.1 Supporting data

The applicant company provided supporting data from a study by Rubio et al (2008), which evaluated the efficacy, safety and tolerability of azithromycin IV and ceftriaxone IV followed by oral azithromycin. This was a 30-day open-label, multicentre non-comparative study. Patients (n = 88) with a diagnosis of moderate to severe CAP were selected for treatment with the study medication to complete a total of ten days (end of treatment [EOT]). Clinical, microbiological and tolerability effects were evaluated at EOT and at 30 days (EOS)[4].

The primary efficacy endpoint was the clinical response at EOS, evaluated and classified as: cure (resolution of signs and symptoms); improvement (resolution of fever but incomplete resolution of other signs and symptoms); or therapeutic failure (no resolution or worsening of any pneumonia signs and symptoms). Of the patients who reached study completion, 82.9% (n = 70) reported cure or improvement (95% confidence interval [CI] = 74.1, 91.7). Safety evaluation was based on all patients who received at least one dose of the study medication (n = 86). Adverse events related to study medication were reported by 33 patients (38.4%)[4].

2.2 Points to note

- No evidence for the clinical effectiveness of azithromycin IV in the treatment of PID was provided by the applicant company[1].
- The company states that the place of azithromycin IV in therapy is as an alternative to clarithromycin IV for the treatment of moderate to severe CAP in combination with other antibiotics in hospitalised patients[1]. In their submission, the applicant company included clarithromycin as a comparator, which is in line with BTS guidelines; however, comparative data are limited[4].
- In the study by Tamm et al (2007), the efficacy and safety of the ceftriaxone plus azithromycin regimen was found to be at least equivalent to clarithromycin; however, this was not specifically powered to demonstrate noninferiority[1,3].
- The study by Tamm et al (2007) was of open-label design, and response was evaluated by an investigator's global assessment of radiological findings and clinical signs and symptoms[3]. The lack of blinding and subjective endpoints may be a source of bias in this study.
- Due to its long half-life, azithromycin may be dosed once-daily to maintain therapeutic plasma levels; for clarithromycin, twice daily doses are necessary[2,15,16].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The applicant company has provided upper and lower estimates of the number of eligible patients (364 and 123, respectively) for treatment with azithromycin IV in Wales[1]. This is based on UK population figures for the number of admissions to an intensive care unit (ICU) for CAP and also the frequency of laboratory confirmed pathogens responsible for CAP in Wales[1,17–19]. The cost comparator provided by the applicant company was clarithromycin IV (Klaricid®). In the treatment of CAP, azithromycin IV or clarithromycin IV would be administered with another antibiotic; however, the additional antibiotic costs have been omitted as the combination therapy would be common to both treatment regimens[1].

The daily dose and duration of therapy is based on guidelines from the Summaries of Product Characteristics (SPCs) and the study conducted by Tamm et al[1–3,15]. The cost has been calculated for the treatment of one episode of CAP so that direct comparison can be drawn, although it is possible that patients may require treatment more than once a year[1]. The company believe that efficacy and treatment-related adverse events are comparable between azithromycin IV and clarithromycin IV and anticipate no additional budgetary impact; consequently, the basic cost of treatment alone has been used in the analysis[1].

Comparative unit costs are given in Table 1. Based on these figures, the cost per treatment is £47.51 less for the azithromycin regimen compared to clarithromycin. Treatment of all eligible patients in Wales would have an approximate yearly expenditure of £6,057–£17,923 for azithromycin compared to £11,900–£35,217 for clarithromycin, a difference of £5,843–£17,294.

3.1.1 AWTTC critique

- The lower estimate of eligible patients in Wales was calculated using UK wide data from the study by Woodhead et al, which covers the period 2000–2004. This did not include data from Scotland and was therefore not taken into account when the lower estimate of the number of patients in Wales was calculated by the applicant company. Also, this figure does not take into account patients treated for CAP in hospital on wards other than ICU. The upper estimate for eligible patients in Wales used 2013 figures for laboratory confirmed infection for pathogens responsible for CAP. These figures may be an overestimation as not all confirmed infections will be in hospitalised patients requiring parenteral antibiotic therapy. Collectively, the company's estimate of the number of patients eligible for treatment is subject to uncertainty.
- The duration of parenteral therapy used by the applicant company was based on regimens used in the study by Tamm et al[3]. It is uncertain whether this would be reflective of Welsh practice.

3.2 Comparative unit costs

Comparative unit costs are given in the table below; these are based on the mean duration of IV and follow-on oral therapy as described in the study by Tamm et al[3]. Based on data for 2012–2013, the applicant company has assumed that the number of laboratory confirmed pathogens responsible for CAP will remain static. In addition, they have assumed that there will not be a significant change in the use of azithromycin IV over the next five years.

Table 1. Example of costs for azithromycin and clarithromycin in the treatment of adult patients with CAP

Treatment option	IV regimen		Follow-on oral regimen		Total cost per treatment
	Dose*	Cost†	Dose*	Cost†	
Azithromycin (maximum dose)	Azithromycin IV (Zedbac®) 500 mg once daily for five days	£47.50	Oral azithromycin 500 mg once daily for five days	£2.90	£50.40
Clarithromycin (maximum dose)	Clarithromycin IV (Klaricid®) 500 mg twice daily for five days	£94.50	Oral clarithromycin 500 mg twice daily for nine days	£3.38	£97.88
Azithromycin (minimum dose)	Azithromycin IV (Zedbac®) 500 mg once daily for two days	£19.00	Oral azithromycin 500 mg once daily for five days	£2.90	£21.90
Clarithromycin (minimum dose)	Clarithromycin IV (Klaricid®) 500 mg twice daily for two days	£37.80	Oral clarithromycin 500 mg twice daily for five days	£1.88	£39.68

*Dosing based on SPCs and a study by Tamm et al[2,3,15,20,21].
†Costs based on Monthly Index of Medical Specialities (MIMS) list prices as of 01 May 2014[22].

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

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

The company do not anticipate that azithromycin (Zedbac®) 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: 24 March 2014
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1 Additional supporting data

Table 1. Summary of additional supportive data

Study	Design	Treatment	No. of clinically evaluable patients	Outcome No. (%) of patients cured at EOS	No. (%) of all patients reporting TEAEs
Plouffe et al (2003)[13]	A prospective, multicentre, open-label trial evaluating efficacy and safety of azithromycin monotherapy in the treatment of patients hospitalised with legionnaires disease.	Azithromycin 500 mg IV for 2–7 days followed by oral azithromycin 1,500 mg for 3–5 days.	23	22 (96)	9 (36)
Plouffe et al (2000)[12]	A multicentre, parallel-group, randomised, open-label trial comparing efficacy and safety of azithromycin monotherapy to cefuroxime (+/- erythromycin) in the treatment of CAP hospitalised patients.	Azithromycin 500 mg IV for 2–5 days followed by oral azithromycin 500 mg for 7–10 days.	130	98 (75)	39 (19.3)
		Cefuroxime 750 mg IV every 8 hours for 2–7 days followed by oral cefuroxime 500 mg every 12 hours for 7–10 days.	122	87 (71)	49 (24.4)
Plouffe et al (2000)[12]	A multicentre, open-label study evaluating efficacy and safety of azithromycin monotherapy in the treatment of CAP hospitalised patients.	Azithromycin 500 mg IV for 2–5 days followed by oral azithromycin 500 mg for 7–10 days.	85	73 (86)	No data
Rubio et al (2008)[4]	A multicentre, open-label trial to evaluate efficacy, safety and tolerability of azithromycin in combination therapy with ceftriaxone in the treatment of CAP hospitalised patients.	Azithromycin 500 mg IV plus ceftriaxone 1 g IV for 2–5 days followed by oral azithromycin 500 mg to complete a total of ten days.	70	58 (82.8)	64 (74.4)
Vergris et al (2000)[14]	A prospective, multicentre, randomised to compare the efficacy and safety of azithromycin monotherapy to cerufoxime plus erythromycin in the treatment of CAP hospitalised patients.	Azithromycin 500 mg IV for 2–5 days followed by oral azithromycin 500 mg to complete a total of 7–10 days therapy.	67	61 (91%)	8 (11.9)
		Cefuroxime 750 mg IV every 8 hours for 2–7 days followed by cefuroxime 500 mg twice daily to a total of 7–10 days therapy plus erythromycin.	78	71 (91%)	38 (48.7)

IV: intravenous; EOS: end of study; TEAE: treatment-emergent adverse event