

EMLc

ATC codes: [J01FA10](#)

Indication	Yaws ICD11 code: 1C5D
INN	Azithromycin
Medicine type	Chemical agent
Antibiotic groups	 WATCH
List type	Core *also listed for single-dose treatment of trachoma and yaws
Formulations	Oral > Liquid: 200 mg per 5 mL oral liquid Oral > Solid: 250 mg (anhydrous) capsule ; 500 mg (anhydrous) capsule
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents . 
Wikipedia	Azithromycin 
DrugBank	Azithromycin 

Expert Committee recommendation

The Expert Committee acknowledged the favourable benefit–harm ratio of single-dose azithromycin as the treatment of choice for yaws and that it is recommended as part of the WHO strategy for yaws eradication. The Committee therefore recommended that the indications for azithromycin on the EML and EMLc be extended to include single-dose treatment of yaws.

Background

Azithromycin is currently available on the EML and EMLc only for single-dose treatment of genital *Chlamydia trachomatis* and of trachoma.

Public health relevance

Yaws is an infectious, neglected tropical disease (NTD) caused by the *Treponema pallidum pertenuis* bacterium. It gives rise to disfiguring cutaneous and skeletal lesions and is spread by skin-to-skin-contact. It primarily affects children living in warm, humid, tropical and impoverished areas (1). The WHO Global Health Observatory data repository reported 13 low- and middle-income countries as being endemic for yaws in 2013 (2). A 2015 systematic review of 27 studies calculated the prevalence of active yaws to range from 0.31% to 14.54% in endemic areas, while the prevalence of latent disease ranged from 2.45% to 31.05%. In the four years to 2013, 256 343 cases were reported, with over 80% from just three countries – Ghana, Papua New Guinea and Solomon Islands (3). In 2012, WHO revised its global eradication policy for yaws and developed the “Morges Strategy” with the goal of eradicating the disease by 2020 (4). New mass drug administration policies were recommended, involving total community treatment and total targeted treatment with oral azithromycin or injected benzathine benzylpenicillin to capture cases and all contacts and achieve rapid interruption of transmission, leading to eradication. It has been estimated that for each clinically

apparent case of yaws, up to six latent cases may exist. Treatment of active cases only has been shown to have limited impact on prevalence after 12 months. In contrast, mass drug administration campaigns have achieved a rapid drop in prevalence (5).

Benefits

Single-dose azithromycin was shown to be non-inferior to single-dose IM benzathine benzylpenicillin in the treatment of yaws in two recent open-label randomized trials (6, 7). In a trial in 250 children in Papua New Guinea, a single oral dose of azithromycin 30 mg/kg (up to 2 g) produced clinical and serological cure of yaws in 96.4% of cases, compared with 92.2% for IM benzathine benzylpenicillin 50 000 U/kg (risk difference (RD) -3.4%; 95% confidence interval (CI) -9.3 to 2.4) and met the prespecified criteria for non-inferiority (6). A similar trial in Ghana involving 353 children yielded similar results. Clinical cure of yaws at 3 weeks was achieved in 98.2% and 96.6% of patients treated with azithromycin and benzathine benzylpenicillin respectively (RD -1.3; 95% CI -4.7 to 2.0) and serological cure at 6 months in 57.5% and 49.1% respectively (RD -8.3; 95% CI -19.1 to 2.4). The prespecified non-inferiority criteria were also met in this study (7). Efficacy of a mass drug administration approach was investigated in a study of 16 092 residents of rural Papua New Guinea (8), 83% of whom were treated with single-dose azithromycin and monitored for one year. The prevalence of active yaws fell by 2.1 percentage points from 2.4% to 0.3% (95% CI 1.9-2.4), and the prevalence of latent yaws with high-titre seroreactivity in children fell by 11.8 percentage points from 18.3% to 6.5% (95% CI 8.9-14.7). The effect was most notable in children aged 1-5 years, with high-titre seroreactivity in this subgroup close to zero one year after treatment. A study conducted in a target population of 15 310 people in Ghana (9) also found reduced prevalence of polymerase chain reaction (PCR)-positive active yaws from 3.1% to 0% (95% CI 2.1-4.4) and of latent yaws from 10.7% to 2.1% (95% CI 6.6-10.9) one year after mass treatment with azithromycin. This study was in press at the time of writing. Cross-sectional surveys in Ghana and the Solomon Islands assessed the impact on yaws of azithromycin mass drug administration for trachoma (10, 11). Each found benefit in terms of ongoing transmission of yaws or post-treatment prevalence of yaws.

Harms

No severe adverse events attributable to azithromycin were identified by means of passive surveillance during a large longitudinal study of 13 490 participants given single-dose azithromycin 30 mg/kg in a mass drug administration for yaws. Active surveillance of 316 participants from 60 households found 54 (17.1%) who reported adverse events (all mild), including 30 (9.5%) with nausea or abdominal pain, 25 (7.9%) with diarrhoea, and 15 (4.7%) with vomiting (8).

Additional evidence

N/A

Cost / cost effectiveness

The application presented a comparison of costs for benzathine benzylpenicillin and azithromycin for yaws based on WHO recommended doses. Taking into account non-drug costs associated with administration of benzathine benzylpenicillin, azithromycin was found to be the cheaper option for the age groups 6-9 and 10-15 years. The application claimed that administration of penicillin is more expensive, requiring more highly trained personnel to administer injections. The application also stated that costs related to acquisition and administration of low-cost generic azithromycin formulations are highly competitive, which offers scope for negotiation of lower prices at country procurement level.

WHO guidelines

Azithromycin given orally is preferred to benzathine benzylpenicillin for the treatment of yaws. The recommended dosage is 30 mg/kg body weight (maximum 2 g) as a single dose by mouth. For children aged under 6 years, syrup is preferable; if this formulation is not available, a tablet should be crushed and mixed with water. Benzathine benzylpenicillin is still effective and relevant in yaws treatment and eradication. Given the operational and logistic problems associated with its administration, however, it may be used as a back-up for people who cannot be treated with, or fail on, azithromycin or in large-scale treatment in places where azithromycin is not available. The standard doses are 0.6 million units for children aged under 10 years and 1.2 million units for people aged 10 years and over.

Availability

Azithromycin is widely available, in many generic versions.

Other considerations

The WHO NTD department strongly supported the application and the inclusion of azithromycin on the EML and EMLc for the treatment of yaws, stating that it is in line with, and will significantly contribute to, the WHO “Morges Strategy” for yaws eradication.

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5. Zahra A. Yaws eradication campaign in Nsukka Division, Eastern Nigeria. *Bull World Health Organ*. 1956;15(6):911–35.
6. Mitja O, Hays R, Ipai A, Penias M, Paru R, Fagaho D et al. Single-dose azithromycin versus benzathine benzylpenicillin for treatment
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