Clarithromycin

Essential medicine status

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.2. Watch group antibiotics

ATC codes: J01FA09

Indication	Helicobacter pylori associated gastric ulcer ICD11 code: DA60.1
INN	Clarithromycin
Medicine type	Chemical agent
Antibiotic groups	WATCH
List type	Core
Additional notes	For use in combination regimens for eradication of H. pylori in adults
Formulations	Oral > Solid: 500 mg
EML status history	First added in 2011 (TRS 965)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Clarithromycin
DrugBank	Clarithromycin

Summary of evidence and Expert Committee recommendations

In 2009, omeprazole was added to the EML, and the Expert Committee requested a review of medicines for the treatment of Helicobacter pylori. Currently, the EML includes omeprazole with a square box, amoxicillin, erythromycin, and metronidazole, used in combination to eradicate H. Pylori. Azithromycin, an alternative antibiotic in some regimens, is listed for infections by Chlamydia trachomatis only. Clarithromycin and tinidazole are not listed. Tetracyclines are listed as eye ointment only. Fluoroquinolones are listed (ciprofloxacin, ofloxacin, levofloxacin). Dr Shanti Mendis, Coordinator from the WHO Chronic Diseases Prevention and Management Department, supported the inclusion of clarithromycin to be used in standard triple therapy. H. pylori infection is the main cause of peptic ulcer. Infection is acquired in infancy and remains life-long unless treated. Approximately half of the world's population is infected by H. pylori, but most have no symptoms or significant complications. The review provided was comprehensive. The Committee noted that there were relatively few data in children. The Committee reviewed the indications where H. pylori eradication has shown benefits. There is high-quality evidence of benefit of eradication of H. pylori in treatment of peptic ulcer as well as in prevention of ulcer recurrence (305); eradication produced long-term cure in more than 80% of patients with duodenal ulcers not associated with NSAIM use. There is no evidence of benefit in patients on long-term NSAIM (306). There is also evidence that H. pylori eradication can reduce recurrent bleeding in patients with bleeding ulcers (307). However, the evidence of benefit is less clear in patients with non-ulcer dyspepsia, and gastro-oesophageal reflux (308). Despite strong epidemiological links between H. pylori infection and gastric cancer, there was conflicting evidence on the benefit of H. pylori eradication on cancer prevention. The Committee considered the evidence supporting combination regimens for H. pylori eradication. International guidelines (North America and European Union) recommend a triple combination of a proton pump inhibitor (PPI) or ranitidine bismuth citrate, and two of three antibiotics (amoxicillin, clarithromycin, or metronidazole) for adults or children. Guidelines do differ in treatment duration: 10–14 days in North America and 7 days in the European Union (309, 310). For

duration of treatment, a comparison of 7 days, 10 days, or 14 days showed no benefit of extending treatment beyond 7 days (311). The Committee then assessed different components of the treatment regimens to determine what should be added to the EML. Based on several meta-analyses, the Committee concluded that PPIs are similarly effective for H. pylori eradication when combined with a variety of different antibiotics. The Committee considered that there was no evidence of differences in efficacy among PPIs (esomeprazole, omeprazole, pantoprazole), but differences in safety profiles, omeprazole and pantoprazole being better tolerated than esomeprazole or rabeprazole. The Committee acknowledged that PPIs have different costs, not supported by differences in effectiveness, and may represent significant costs in health care budgets. The Committee therefore confirmed that omeprazole with a square box be maintained in the EML. The Committee noted that amoxicillin given twice daily is as effective as four times daily (2 g/day) for H. pylori eradication (312). In children a dose of 50 mg/kg per day was found effective. In case of penicillin allergy, substitution with clarithromycin or a quinolone is possible. Among macrolides, clarithromycin and azithromycin, but not erythromycin, have been studied in H. pylori infections. The Committee noted that H. pylori resistance to clarithromycin has increased, which may be explaining decreased cure rates (<80%) after first-line therapy. A study performed in Tunisia showed resistance levels of 14.6% and 56.8% in adults, and 18.8% and 25% in children for clarithromycin and metronidazole, respectively (313). The choice of first-line treatment should therefore be based on local resistance patterns. Clarithromycin doses of 500 mg twice daily (or modified release 1 g/day) have been used successfully for H. pylori eradication, but a comparison of doses of 400 mg and 800 mg per day produced similar cure rates. In children a dose of 15 mg/kg has been found effective. Azithromycin-based regimens may have advantages in terms of adverse events but there is some uncertainty concerning efficacy. The Committee noted the high level of H. pylori resistance to tetracycline in studies (up to 38% in a study in Iran in 2009) which may reduce its potential benefit. Costs of treatment were evaluated. In developed countries, a comparison of different triple therapies to H2 antagonists maintenance was conducted. Although a bismuth-based triple therapy for 14 days was cheaper than a PPI-based triple therapy for 7 days, both were cheaper and more effective (US$ 223–410, with recurrence prevention of 70–86%) than H2 antagonists maintenance (US$ 425, 72% recurrence prevention) (314). Other data show that two regimens were the most cost effective (compared to four other combinations), a triple combination of omeprazole, clarithromycin, and amoxicillin, and a quadruple one of ranitidine, metronidazole, amoxicillin, and bismuth, producing eradication rates and costs of 90% at €195.8, and 90% at €158.7, respectively (315). From International Buyer Prices, a 7-day clarithromycin treatment (1 g/day) would cost between approximately US$ 5.52 and US$ 6 and omeprazole (20 mg/day) about US$ 0.92 (price in Costa Rica). The Committee reviewed the evidence relating to bismuth salts. The inclusion of bismuth in a triple combination (with tetracycline and PPI) resulted in higher cure rates than a triple combination (clarithromycin with amoxicillin and PPI) but more severe adverse effects were reported in the bismuth group (316). The Committee noted that the addition of bismuth could overcome clarithromycin resistance in quadruple combinations. However, the Committee also considered that the availability of bismuth salts was limited in many countries, where regulatory action has resulted in its withdrawal for safety reasons. In summary, the Committee concluded that clarithromycin should be added to the EML, specifically for use in H. pylori eradication regimens, that metronidazole should be maintained on the List for this purpose in addition to the existing indications, but that there was no reason to include bismuth salts or azithromycin at this time. There was insufficient evidence of clinical benefit to justify inclusion on the EMLc at this time. Choice of treatment regimen should be based on national guidelines, with due consideration of local resistance patterns, availability, and cost. References: 305. Ford AC et al. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. Cochrane Database of Systematic Reviews, 2003, (4):CD003840. 306. Kiltz U et al. 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