Ivermectin

Essential medicine status

Section: 6. Anti-infective medicines > 6.1. Anthelminthics > 6.1.1. Intestinal anthelminthics

EMLc | ATC codes: P02CF01

Indication	Hookworm diseases ICD11 code: 1F68
INN	Ivermectin
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid: 3 mg tablet (scored)
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	Ivermectin
DrugBank	Ivermectin

Expert Committee recommendation

The Expert Committee acknowledged the favourable benefit–harm ratio and the public health impact of ivermectin in the treatment of intestinal helminth infections. The Committee recommended adding ivermectin to the EML and EMLc under Section 6.2.1 Intestinal anthelminthics for use against Strongyloides stercoralis and soil-transmitted helminthiasis. It may be used in combination with albendazole for treatment of soil-transmitted helminthiasis.

Background

Currently, the EML and EMLc include ivermectin 3-mg scored tablet as an antifilarial (Section 6.1.2).

Public health relevance

Target 3.3 of the Sustainable Development Goals is to end, by 2030, the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and to combat hepatitis, waterborne diseases and other communicable diseases. Strongyloidiasis Strongyloidiasis is globally distributed and is endemic in the tropics and subtropics (1, 2). An estimated 30–100 million people are infected worldwide; there are no precise data on prevalence in endemic countries. In low- and middle-income countries, strongyloidiasis is endemic; children are at highest risk of chronic infection. Parasitic worm infections are associated with malnutrition and, in children, with impaired growth and cognitive development and poor school performance. Heavy worm infection in children is associated with anaemia. Soil-transmitted helminthiasis The global target is to eliminate morbidity due to soil-transmitted helminthiasis in children by 2020. This will be achieved by treating at least 75% of children (an estimated 873 million) in endemic areas (3). The soil-transmitted helminthiasis disease cluster is considered to be the most widespread of the neglected tropical diseases worldwide. The most recent estimates indicate that close to 1.5 billion people are infected with Ascaris lumbricoides (roundworm), Trichuris trichiura (whipworm), Necator americanus and/or Ancylostoma duodenale (hookworms) in more than 100 endemic countries (4, 5). Some 3.3 million disability-adjusted life years (DALYs), resulting from symptomatic infection, wasting, mild abdominopelvic

problems and anaemia, are attributed to soil-transmitted helminthiasis infection (4, 6). The highest risk groups are children, who are in a critical phase of growth and development, and women of childbearing age, including pregnant women, who have increased nutritional requirements during pregnancy and lactation (7).

Benefits

Strongyloidiasis The application presented the results of a 2016 Cochrane systematic review (8) that included four studies comparing ivermectin with albendazole. Two of the four studies included adults and children (9, 10). The results showed that parasitological cure was higher with ivermectin (risk ratio (RR) 1.79; 95% confidence interval (CI) 1.55–2.08; 478 participants; moderate-quality evidence – downgraded for risk of bias (two trials did not use allocation concealment and no description of allocation method was provided)). In the same review, three trials compared ivermectin with tiabendazole. The results showed little difference in parasitological cure (RR 1.07; 95% CI 0.96–1.20; 467 participants; low-quality evidence). The review found that single-dose ivermectin (200 µg/kg) was associated with the same rate of parasitological cure as two-dose ivermectin treatment (RR 1.02; 95% CI 0.94–1.11). However, it noted that this result was based on only two trials with a small number of participants (n = 94). Soil-transmitted helminthiasis The application presented data for the efficacy of ivermectin alone and co-administered with albendazole against soil-transmitted helminths from eight randomized controlled trials identified by literature search (9, 11–16). Cure rates (CRs) and egg reduction rates (ERRs, when available) were extracted for each treatment against A. lumbricoides, T. trichiura and hookworms. Notably, not all studies evaluated efficacy of the drugs against all soil-transmitted helminthiases. Belizario et al. (11) and Knopp et al. (13) reported that albendazole–ivermectin is not more effective at eliminating A. lumbricoides than albendazole alone. These two studies revealed a CR of 79.8% against A. lumbricoides infections for the albendazole–ivermectin combination versus 73.5% for albendazole alone. In terms of intensity, they observed ERRs of 100% and 99.9% for the co-administration versus 99.9% and 100% for albendazole alone. Meta-analysis of three studies (11–13) which compared albendazole–ivermectin with albendazole alone including 342 patients revealed co-administration of albendazole–ivermectin to be more effective at eliminating T. trichiura infection than albendazole alone (CR 47%, RR 0.53; 95% CI 0.3–0.76). In these studies, ERR ranged from 91.3% to 99.7% for albendazole–ivermectin and from 40.3% to 97.2% for albendazole alone. One study evaluated the efficacy of albendazole–ivermectin against hookworm infections (13). The results indicated that the combination is more effective in curing hookworms than albendazole alone. The difference in ERRs, however, was small – 95.9% with the combination and 94% with albendazole alone. Four other studies compared the efficacy of ivermectin alone against T. trichiura (CR 52.7%; ERR from 58.9–98.2%) (11, 15-17); A. lumbricoides (CR 90.3%; ERR 100%) (11, 15, 16); and hookworms (CR: 24.6%; ERR reported in one study as 80%) (15–17). The application concluded that the evidence showed ivermectin to be a highly efficacious treatment for strongyloidiasis, with greater efficacy than albendazole, mebendazole and tiabendazole and increased efficacy in children under 5 years of age. For soil-transmitted helminthiases, the application stated that ivermectin administered with albendazole is more efficacious than albendazole alone in treating T. trichiura; for treatment of A. lumbricoides and hookworm, treatment with the combination is largely comparable to albendazole alone.

Harms

Strongyloidiasis In the four studies comparing ivermectin with albendazole included in the Cochrane systematic review (8), there were no statistically significant differences in adverse events (RR 0.80; 95% CI 0.59–1.09; 518 participants; low-quality evidence). In the three trials comparing ivermectin with tiabendazole, adverse events were less common with ivermectin (RR 0.31; 95% CI 0.20–0.50; 507 participants; moderate-quality evidence). Dizziness, nausea and disorientation were commonly reported in all drug groups. There were no reports of serious adverse events. Zaha et al. (18) found significant liver abnormalities in two ivermectin dosage groups. In the 110µg group, a rise in glutamic pyruvic transaminase (GPT) or glutamic oxaloacetic transaminase (GOT) was observed in 6.9% (19/274) of the patients whose liver function was normal before treatment. In the 200-µg group, liver dysfunction was observed in 6.5% (6/92) of patients. The abnormalities in both groups were mild, transient and not clinically important. Soil-transmitted helminthiasis Four studies compared the safety of co-administered albendazole–ivermectin with that of albendazole alone (13, 19–21). Co-administration was associated with more adverse events than either albendazole or ivermectin alone; this was not significant in either case (19, 20). The frequency and severity of adverse events have been shown to be associated with baseline infection status, intensity of infection and infection-related immune response parameters. For example, when administered to subjects with high Loa loa microfilaraemia, ivermectin has been associated with severe adverse reactions such as neurological signs, encephalopathy and coma (22). In case of confirmed loiasis hyper-endemicity, alternative treatment schemes should be considered. Of a total of 1656 reports for ivermectin in VigiBase, 525 (31.7%) – mostly (397) from Sierra Leone

– contained both ivermectin and albendazole. Between 2007 and 2015, more than 33 million tablets of ivermectin have been administered with albendazole in the lymphatic filariasis programme, giving rise to approximately 11 adverse events per one million treatments during that period. All reported adverse events were considered minor. The most commonly reported adverse reaction for ivermectin alone or with albendazole were pruritus, headache, dizziness, vomiting, urticarial rash and diarrhoea. In total, there were 459 reports of ivermectin having caused a serious adverse reaction; there were 63 deaths (probably due to causes other than ivermectin itself). Concomitant medication was frequently administered. The most frequent adverse reaction reported in cases that resulted in death included strongyloidiasis, drug ineffectiveness, pneumonia, pyrexia, multiple organ dysfunction syndrome, acute respiratory distress syndrome, cardiac arrest, septic shock, Stevens–Johnson syndrome, thrombocytopenia and toxic epidermal necrolysis. Full assessment of the health status of individuals before treatment to exclude seriously ill individuals is recommended (7). It is recommended that ivermectin not be administered to children less than 90 cm tall or weighing less than 15 kg, pregnant women, lactating women in the first week after birth or severely ill individuals.

Additional evidence

N/A

Cost / cost effectiveness

According to the MSH (Management Sciences for Health) International Medical Products Price Guide in 2013, the median buyer price per 3-mg tablet of ivermectin was US$ 0.0296 (23). For large-scale treatment of soil-transmitted helminthiasis infection, the application asserted that adding ivermectin to albendazole that is already being delivered for mass drug administration programmes would involve only marginally increased costs, namely those associated with ivermectin purchase, and would have ancillary benefits for strongyloidiasis in co-endemic areas.

WHO guidelines

WHO's Preventive chemotherapy in human helminthiasis. Coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers recommends ivermectin and albendazole as treatment options for strongyloidiasis. Ivermectin is not currently among the recommended medicines (albendazole or mebendazole) for treatment of soil-transmitted helminthiasis (7).

Availability

Ivermectin has wide market availability. Ivermectin 3-mg tablet was included on the Invitation for Expression of Interest for WHO prequalification in July 2015. The product is not currently prequalified.

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