Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim

EMLc | ATC codes: J04AC51

Indication	Other specified prophylactic measures ICD11 code: QC05.Y
INN	Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 300 mg + 25 mg + 800 mg + 160 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	Read more about patents.
Wikipedia	Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim
DrugBank	Isoniazid, Pyridoxine, Sulfamethoxazole, Trimethoprim

Expert Committee recommendation

The Expert Committee recommended the inclusion of the fixed-dose combination formulation of isoniazid, pyridoxine, sulfamethoxazole and trimethoprim (co-trimoxazole) on the core list of the EML and EMLc. Listing was recommended in a new subsection (6.4.2.5) for medicines for the prevention of HIV-related opportunistic infections. The Committee considered that the availability of FDC formulations offers the benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence. The Committee also noted the direct evidence supporting effectiveness of the FDC from the REALITY trial. The FDC was based on well-established dosing combinations.

Background

The application requested addition of a fixed-dose combination formulation of isoniazid, pyridoxine, sulfamethoxazole and trimethoprim to the core list of EML and EMLc for the prevention of infections in adults and children living with HIV/AIDS. WHO included this fixed-dose combination (FDC) of isoniazid (INH), pyridoxine (vitamin B6), sulfamethoxazole and trimethoprim (co-trimoxazole, CTX) in the 10th Invitation for Expression of Interest for prequalification of HIV medicinal products. A formulation manufactured by Cipla Ltd was added to the list of prequalified medicines on 21 December 2016. Current WHO consolidated guidelines recommend both CTX preventive therapy (CPT) and INH preventive therapy (IPT) as part of the standard package of care available to prevent tuberculosis (TB), toxoplasmosis, pneumocystis, bacterial pneumonia, malaria and isosporiasis, and reduce mortality and hospitalizations among adults and children living with HIV/AIDS on the condition that active TB has been excluded (1). Vitamin B6 is recommended in all HIV-infected persons on INH to prevent peripheral neuropathy

and other INH toxicities.

Public health relevance

HIV infection increases the risk of TB 20–37-fold, depending on the severity of the HIV epidemic (2). WHO estimated that 10.4 million people developed TB in 2015, including 1.2 million persons living with HIV (PLHIV). TB was one of the top 10 causes of death worldwide in 2015 and responsible for more deaths than HIV and malaria. In 2015, 1.8 million people died from TB, including 0.4 million among PLHIV (3). The target population for this FDC is PLHIV in whom active TB has been excluded.

Benefits

CTX for prevention of Pneumocystis jirovecii pneumonia (PCP) and other opportunistic infections and INH plus vitamin B6 supplementation for TB have been evaluated and used in clinical practice for many years. The INH/B6/CTX FDC was used as part of a clinical trial (the REALITY study) conducted in 1805 African patients, including 72 paediatric patients (aged 5–17 years) (4). Other use of the product has not been documented as the FDC is only now becoming commercially available. The open-label REALITY trial (Reduction of EArly mortaLITY in HIV-infected adults and children starting antiretroviral therapy (ART)) was conducted to evaluate whether an enhanced package of infection prophylaxis at the time of ART initiation would reduce mortality in an African population. The study randomized ART-naive HIV-infected adults and children aged 5 years and above with CD4 <100 cells/mm3 to initiating ART with enhanced prophylaxis (continuous CTX plus 12 weeks' INH/B6 (antituberculosis) and fluconazole (anticryptococcal/anticandidiasis), 5 days' azithromycin (antibacterial/antiprotozoal) and single-dose albendazole (anthelminthic), versus standard-of-care co-trimoxazole. INH/B6/CTX was formulated as a scored FDC tablet. The study investigators concluded that, in HIV-infected adults and children over 5 years of age with CD4 <100 cells/mm3 enhanced prophylaxis at ART initiation, reduced early mortality from 14.4% to 11.0% over 96 weeks (25% relative reduction), and reduced adverse events and hospitalizations. The additional pill burden did not adversely affect viral load suppression and was reduced by a well-accepted FDC of CTX/INH/B6. The authors concluded that policy-makers should consider adopting and implementing this low-cost, broad infection prevention package, which could save 3.3 lives for every 100 individuals treated (4). The results of the REALITY study are supportive of the use of INH/B6/CTX FDC in HIV-infected adults. The small number of paediatric patients enrolled in the study makes it difficult to interpret efficacy results in patients aged 5–17 years, but the available data support use of a half-dose in patients under 12 years of age and weighing least 14 kg and use of the full dose in patients aged 12–17 years. A review and commentary published in 2015 summarized the need for an FDC product that would include all the components of IPT and CPT in a single tablet (5). The authors concluded that IPT is a useful adjunct to ART in preventing TB in settings of high TB transmission but that long-term treatment is needed to maintain ongoing benefits. They found no evidence to suggest that IPT increased the risk of INH-resistant TB. In addition, they noted that CPT reduced mortality by 60% if started with ART at CD4 counts of 350 cells/mm3 or lower, regardless of geographical region. They noted that the benefits of continuing CPT were further supported by a randomized trial in Uganda and Zimbabwe of children infected with HIV, which showed that those who continued CPT after 2 years of ART had reduced hospitalizations for malaria, pneumonia, sepsis and meningitis.

Harms

All the component drugs of the INH/B6/CTX FDC have well-characterized toxicity and tolerability profiles. The combination of these drugs into the bioequivalent FDC does not alter the toxicity profile but is expected to improve tolerability by reducing pill burden. A number of relevant drug–drug interactions are associated with the medicines included in the FDC, but these also apply to the medicines administered separately.

Additional evidence

A systematic review of 10 randomized controlled trials (7619 patients) comparing IPT with placebo in HIV-infected adults found that IPT was associated with a reduced risk of TB among all participants (relative risk (RR) 0.65; 95% confidence interval (CI) 0.51–0.84). IPT was also associated with a reduced risk of HIV disease progression among all participants (RR 0.69; 05% CI 0.48–0.99) (6). A Cochrane systematic review of four randomized trials (1476

patients) comparing CTP with placebo in HIV-infected adults found that CTP was associated with a reduced risk of mortality (RR 0.69; 95% CI 0.55–0.87), morbid events (RR 0.76; 95% CI 0.64–0.9) and hospitalization (RR 0.66; 95% CI 0.48–0.92) (7).

Cost / cost effectiveness

There is no information on the cost of this FDC; however, the application estimates a cost of about US$15 per adult patient per year. A number of economic analyses have considered the cost–effectiveness of elements of the proposed FDC. Yazdanpanah et al. reported that using CPT would cost US$ 200/life-year gained (8). Shrestha et al. used a Markov model to estimate the cost–utility of treating patients with INH for nine months, regardless of purified protein derivative (PPD) status, and arrived at a figure of US$ 106/quality-adjusted life-year (QALY) gained in Uganda. These authors found that this treatment approach would produce an additional 30 QALYs per 100 patients treated (9). Bell et al. used a Markov model to estimate that 6 months of IPT would save US$ 24 per primary or secondary case prevented (considering medical care and societal costs), increase life expectancy and quality-adjusted life expectancy, and reduce TB incidence (10). In addition, the application argued that there may be cost savings related to the shipment and storage of FDC tablets and that a reduced pill burden for patients would improve compliance.

WHO guidelines

The WHO 2016 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection contain recommendations for the use of drugs for prevention and treatment of opportunistic infections such as PCP and serious bacterial infections (1). The Guidelines offer recommendations on CPT for HIV-infected adults, adolescents, children and infants. The guidelines note that all HIV-infected adults, adolescents and children should be clinically screened for TB to identify those who should be either expedited for TB diagnosis or given preventive TB therapy. In the absence of a clinical suspicion of active TB, HIV-infected patients should be offered IPT. Pyridoxine is recommended in all HIV-infected persons on INH to mitigate toxicity.

Availability

This FDC is currently being manufactured by Cipla Ltd. It received WHO prequalification status on 21 December 2016. All the component medicines of INH/B6/CTX are off-patent and available from many generic suppliers. The FDC is currently under review by some national regulatory agencies; at the time of writing, however, it had not been reviewed by either the U.S. Food & Drug Administration or the European Medicines Agency.

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5. Harries AD, Lawn SD, Suthar AB, Granich R. Benefits of combined preventive therapy with co-trimoxazole and isoniazid in adults living with HIV: time to consider a fixed-dose, single tablet coformulation. Lancet Infect Dis. 2015;15(12):1492–6.
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