Sulfadoxine + pyrimethamine

Essential medicine status ✓

ATC codes: P01BD51

Indication	Malaria due to Plasmodium falciparum ICD11 code: 1F40
INN	Sulfadoxine + pyrimethamine
Medicine type	Chemical agent
List type	Core
Additional notes	For intermittent preventive treatment in pregnancy (IPTp)
Formulations	Oral > Solid: 500 mg + 25 mg tablet
EML status history	First added in 2019 (TRS 1021)
Sex	Female
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	Sulfadoxine + pyrimethamine
DrugBank	Sulfadoxine, Pyrimethamine

Expert Committee recommendation

The Expert Committee recommended the listing of sulfadoxine + pyrimethamine 500 mg + 25 mg fixed-dose combination tablet on the core list of the EML for the new indication of intermittent preventive treatment of malaria in pregnancy (IPTp) on the basis of demonstrated efficacy in terms of improved outcomes for mothers and newborns, and acceptable safety, and in alignment with WHO malaria treatment guidelines. The Expert Committee noted the lack of evidence of the impact of the use of SP-IPTp on antimicrobial resistance, and encouraged further assessment and monitoring in this regard within programme delivery.

Background

The application requested listing of sulfadoxine + pyrimethamine (SP) fixeddose combination tablet on the core list of the EML for the new indication of intermittent preventive treatment (of malaria) in pregnancy (IPTp). Sulfadoxine + pyrimethamine 500 mg + 25 mg tablets are currently included on the EML and EMLc for use in combination with artesunate 50 mg for the curative treatment of malaria.

Public health relevance

Malaria is one of the leading causes of illness, death, and lost economic productivity globally. While there has been successful scale up and use of critical commodities, malaria still resulted in over 219 million cases and more than 435 000 deaths in 2017; most of the deaths occurred in children under 5 years of age and pregnant women (1). In sub-Saharan Africa (SSA), over 30 million pregnant women are annually exposed to infection from malaria (2). Of these, an estimated 10 000 pregnant women and up to 200 000 newborns die from malaria in pregnancy (MiP), primarily due to infection with Plasmodium falciparum (3). Furthermore, recent data

indicate that up to 20% of stillbirths in SSA are attributable to MiP (4). WHO recommends that IPTp-SP be given to all pregnant women at each antenatal care visit, starting as early as possible in the second trimester (i.e. not during the first trimester) (5). Each IPTp-SP dose should be given at least one month apart, with at least three doses during each pregnancy. The expected benefits of IPTp-SP include: –– Prevention of the adverse consequences of malaria on maternal and fetal outcomes, such as placental infection, clinical malaria, maternal anaemia, fetal anaemia, low-birth-weight and neonatal mortality (6). –– A cost-effective intervention for both prevention of maternal malaria and reduction of neonatal mortality in areas with moderate or high malaria transmission (7). –– Protection against both neonatal mortality (protective efficacy 18%) and low-birth-weight (21% reduction) under routine programme conditions (8). To date, 39 African countries have adopted this policy. However, there is an unacceptably low proportion of eligible pregnant women receiving IPTp with quality-assured SP: only an estimated 22% of pregnant women received three doses of IPTp-SP in 2017 (1). It has been estimated that if all women with at least three antenatal care visits in Africa received IPTp-SP, that an additional 215 000 (95% credible interval (crI) 128 000 to 318 000) low-birth-weight deliveries could be prevented (9).

Benefits

The application presented the findings of a systematic review of seven trials (6281 pregnancies) in which a direct comparison of two doses of IPTp-SP with three or more doses at least one month apart was evaluated (10). The trials were conducted in Burkina Faso, Kenya, Malawi, Mali and Zambia between 1996 and 2008. In comparison with two doses of SP, three or more doses was associated with: ■ increased mean birth weight by an average of 56 g (95%CI 29 to 83; seven trials, 2190 participants, high quality evidence); ■ fewer low-birth-weight infants by about 20% (relative risk (RR) 0.80; 95%CI 0.69 to 0.94; absolute risk reduction, 33 per 1000 (95%CI 10 to 52); NNT = 31; seven trials, 2190 participants, high quality evidence); ■ reduced placental parasitaemia by about 50% (RR, 0.51; 95%CI 0.38 to 0.68; absolute risk reduction, 31 per 1000 (95%CI 20 to 39); six trials, 1436 participants, high quality evidence); and ■ reduced maternal parasitaemia by about 33% (RR, 0.68; 95%CI 0.52 to 0.89; seven trials, 2096 participants, moderate quality evidence). The reduction in risk for low-birth-weight was consistent for a wide range of levels of resistance to SP.

Harms

There were no differences in rates of serious adverse events between treatment groups in the systematic review mentioned above (10). IPTp-SP is generally very well tolerated. Mild and transient side-effects including nausea, vomiting, weakness and dizziness have been reported by some women, particularly with the first dose. Studies have demonstrated that sideeffects tend to decrease with the administration of further doses (11, 12). The adverse effects reported are mainly those associated with sulfonamides, including gastrointestinal disturbances, headache, dizziness and skin reactions such as photosensitivity, rash, pruritus, urticaria and slight hair loss (13–16). Potentially fatal skin reactions, namely erythema multiforme, Stevens– Johnson syndrome and toxic epidermal necrolysis, have also been reported. Demonstrated drug–drug interactions have been observed between SP and high doses (>5 mg) folic acid resulting in reduced efficacy of SP (17). Concurrent use with trimethoprim, alone or in combination with sulfamethoxazole should be avoided due to increased risk of severe cutaneous reactions (18). There is limited evidence of potential teratogenicity when SP is used during the first trimester of pregnancy (13, 19). Use of SP during the first trimester is not recommended.

Cost / cost effectiveness

SP is an inexpensive medicine, and most countries already have a delivery system for IPTp-SP in place, which is often integrated into a comprehensive focused antenatal care (FANC) package. In comparison to placebo, in Mozambique, delivery of two doses of IPTp-SP has been estimated to cost US$ 41.46 (95%CI 20.50 to 96.70) per maternal outpatient visit averted. This same study estimated an incremental cost effectiveness ratio (ICER) of US$ 1.08 (95%CI 0.43 to 3.48) per disabilityadjusted life-year (DALY) averted (7). Additionally, using data from seven countries, the incremental cost-effectiveness of three or more doses of IPTp-SP (compared to two doses) has been estimated at US$ 7.28 (20). The WHO recommendations on intermittent screening and treatment in pregnancy and the safety of ACTs in the first trimester (21) state that IPTp-SP remains highly cost-effective in preventing the adverse consequences of malaria on maternal and fetal outcomes, and should therefore be actively scaled up in line with the current WHO recommendations. The threshold level of malaria transmission below which IPTp-SP is no longer cost-effective has not been identified. Therefore, in areas where IPTp-SP is implemented and transmission has been reduced to low

levels as a result of successful control strategies, WHO recommends continued IPTp-SP implementation until the area approaches interruption of transmission.

WHO guidelines

The 2015 WHO Guidelines for the treatment of malaria (5) make the following recommendation regarding IPTp-SP: In malaria-endemic areas in Africa, provide IPTp-SP to all women in their first or second pregnancy as part of antenatal care. Dosing should start in the second trimester and doses should be given at least one month apart, with the objective of ensuring that at least three doses are received (strong recommendation, high quality evidence).

Availability

Quality assured sulfadoxine + pyrimethamine 500 mg + 25 mg tablets are available from Guilin Pharmaceuticals (China) with WHO prequalification status. Quality-assured sulfadoxine + pyrimethamine 500 mg/25 mg tablets are also available from Remedica Pharmaceuticals (Cyprus).

Other considerations

Starting as early as possible in the second trimester, IPTp-SP is recommended for all pregnant women at each scheduled antenatal care visit until the time of delivery, provided that the doses are given at least one month apart. IPTp-SP should ideally be administered as directly observed therapy (DOT) of three tablets sulfadoxine + pyrimethamine 500 mg + 25 mg giving the total required dosage of 1500 mg + 75 mg SP.

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