Does the application adequately address the issue of the public health need for the medicine?

Yes

The fixed-dose combination of sulfamethoxazole 800mg and trimethoprim 160mg (co-trimoxazole, CTX), isoniazid (INH) 300mg, and pyridoxine (Vitamin B6) 25 mg, is proposed. It will prevent tuberculosis, toxoplasmosis, pneumocystosis, bacterial pneumonia, malaria, and isosporiasis; and reduce mortality and hospitalizations among adults and children living with HIV/AIDS (PLHIV).

The efficacy of CPT and IPT are compromised by lapses in adherence. Fixed-dose combinations have the potential to improve adherence and reduce the pill burden.

Have all important studies that you are aware of been included in the application?

Yes

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes


The results of the REALITY study are highly supportive of the use of CTX/INH/B6 FDC in HIV-infected adults.
The small number of pediatric patients enrolled in the study makes it difficult to interpret efficacy results in patients 5 to 17 years of age but the available data support use of the half dose in patients < 12 years of age and at least 14 kg and use of the full dose in patients 12 to 17 years of age.

(4) Is there evidence of efficacy in diverse settings and/or populations?  
No

All components have been widely used for several decades in various international health settings.

(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?  
Yes

Safety profile of the components is well known. CTX/INH/B6 FDC is contraindicated in persons who have developed severe hypersensitivity reactions to any of the component drugs. Isoniazid is contraindicated in patients with acute liver disease or a history of previous isoniazid associated hepatic injury.

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?  
No

None needed beyond those required for adequate diagnosis and evaluation of active TB.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)  
Yes
The CTX/INH/B6 FDC is currently under review by the WHO Pre-qualification Program and some national regulatory agencies. It has not been reviewed by either the U.S. FDA or EMA.

Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes

WHO had listed this fixed-dose combination in the 10th Invitation for Expression of Interest for HIV medicinal products. The WHO’s Consolidated Guidelines recommend that countries’ HIV programs provide IPT as part of the package of care for PLHIV when active tuberculosis is safely excluded. This recommendation also states that use of antiretroviral drugs does not preclude the use of IPT. Pyridoxine (B6) is recommended in patients on isoniazid as it is a benign intervention which prevents peripheral neuropathy and other isoniazid toxicities. CPT is also recommended as part of the package of care provided by countries for PLHIV. "Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach.” World Health Organization. June, 2016, ISBN: 978 92 4 154968 4

Please comment briefly on issues regarding cost and affordability of this medicine.

The fixed-dose combination tablet comprised of sulfamethoxazole 800 mg, trimethoprim 160 mg, isoniazid 300 mg, and pyridoxine 25 mg (CTX/INH/B6 FDC) for adult and adolescent patients (over 25 kg) is manufactured by Cipla. The oval/capsule shaped tablet is scored, enabling children between 14 kg and 25 kg to receive half tablets. Use of the CTX/INH/B6 FDC might be expected to cost about $15 per adult patient per year.

Any additional comments?

The fixed-dose combination is a beneficial adjunct but it should be used advisedly.
I propose the inclusion FDC SCORED TABLET CONTAINING
SULFAMETHOXAZOLE 800 mg / TRIMETHOPRIM 160 mg /
ISONIAZID 300 mg & PYRIDOXINE 25 mg in the 20th WHO Model
List of Essential Medicines as well as in the children list.
It is to be included under: “Other Antibacterials” section 6.2.2