Application to add itraconazole and voriconazole to the essential list of medicines for treatment of fungal diseases

– Support document
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1. **Summary statement of the proposal for inclusion, change or deletion**
   As a growing trend of invasive fungal infections has been noticed worldwide, available few antifungal drugs requires to be used optimally. Invasive aspergillosis, systemic candidiasis, chronic pulmonary aspergillosis, fungal rhinosinusitis, allergic bronchopulmonary aspergillosis, phaeohyphomycosis, histoplasmosis, sporotrichosis, chromoblastomycosis, and relapsed cases of dermatophytosis are few important concern of southeast Asian regional area. Considering the high burden of fungal diseases in Asian countries and its associated high morbidity and mortality (often exceeding 50%), we support the application of including major antifungal drugs against filamentous fungi, itraconazole and voriconazole in the list of WHO Essential Medicines (both available in oral formulation). The inclusion of these oral effective antifungal drugs in the essential list of medicines (EML) would help in increased availability of these agents in this part of the world and better prompt management of patients thereby reducing mortality. The widespread availability of these drugs would also stimulate more research to facilitate the development of better combination therapies.

2. **Name of the WHO technical department and focal point supporting the application (where relevant)**
   Not applicable

3. **Name of the organization(s) consulted and/or supporting the application**
   WHO collaborating centre for reference and research of fungi of medical importance, Centre of Advanced Research, Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh-160012, India
   - Arunaloke Chakrabarti ([arunaloke@hotmail.com](mailto:arunaloke@hotmail.com))
   - Shivaprakash M Rudramurthy ([mrshivprakash@yahoo.com](mailto:mrshivprakash@yahoo.com))
   - Anup Ghosh ([anupkg3@gmail.com](mailto:anupkg3@gmail.com))
   - Harsimran Kaur ([drharsimranpgi@gmail.com](mailto:drharsimranpgi@gmail.com))

4. **International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine**
5. **Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate).**
   As per the document submitted by David Denning

6. **Whether listing is requested as an individual medicine or as a representative of a pharmacological class**
   Individual medicines under EML section 6.3 Antifungal medicines.

7. **Treatment details (requirements for diagnosis, treatment and monitoring)**
   As per the document submitted by David Denning

8. **Information supporting the public health relevance and Review of benefits: summary of comparative effectiveness in a variety of clinical settings**
   Fungal infections are often undiagnosed and untreated due to lack of awareness. They are responsible for 1.5 million deaths per year close to tuberculosis (1.4 million) and malaria (1.24 million) which are well known global “hidden killers”. [1]. Asian continent, comprising of world’s half population has a very favourable environment for growth of fungi. Few reports indicate very high incidence of invasive fungal infections in Asian countries. Moreover, there is constant increase in susceptible groups of populations including hematology malignancy with chemotherapy, transplant patients, chronic liver and renal diseases and critically ill patients. Clinicians are facing huge challenge of tackling these infections due to delay in management and scarcity of antifungal drugs in this part of the world. The drugs itraconazole and voriconazole have broad spectrum of action in variety of fungal diseases prevalent in our Asian continent. Though invasive fungal infections are important cause of morbidity and mortality in large number of patients, those two regularly used drugs are not included in the essential drugs list of WHO. In support of this need, few examples are provided.

   **Invasive aspergillosis:** Global Comparative Aspergillus Study (GCAS) compared voriconazole to amphotericin B (AmB) deoxycholate for the primary therapy of
invasive aspergillosis (IA). [2] A higher favourable 12-week response rate (54.7% versus 29.9%) and survival rate (70.2% versus 54.9%) was demonstrated for voriconazole in comparison to AmB. They also demonstrated a high response rate even in possible IA treated with voriconazole vs AmB (26.2% vs 24.3%). The authors confirmed the higher efficacy of voriconazole over AmB deoxycholate in mycological documented IA. However, antifungals prescribed in invasive aspergillosis in developing countries usually include amphotericin B deoxycholate and itraconazole due to economic concerns regarding liposomal amphotericin B, voriconazole and caspofungin. [3]

**Chronic pulmonary aspergillosis (CPA):** CPA is a significant problem in Asia due to higher burden of tuberculosis in this region. The 5-year prevalence of CPA is estimated to be 23.1 and 16.2 million per 10000 populations in India and China respectively. [4] The drugs approved by IDSA for these diseases are either voriconazole or itraconazole. [5]. Agarwal et al observed itraconazole to be superior to standard supportive treatment alone in stabilising cases of chronic cavitary pulmonary aspergillosis (CCPA). [6] The number of patients showing overall response was significantly higher in the itraconazole group (76.5%) vs. the control (35.7%) group (P = 0.02). The numbers of patients demonstrating clinical or radiological response were also significantly higher in the itraconazole group (P = 0.016 and 0.01 respectively). Saito et al showed a good response in 60% patients with CPA who were given voriconazole. [7]

**Allergic fungal rhinosinusitis (AFRS):** Currently, AFRS is responsible for 7%–12% of CRS cases undergoing sinus surgery [8]. Of the total cases of CRS, FRS is observed in 27.2% cases (1.1 persons per 1000 population) in India indicating high burden of FRS cases in rural northern India [9]. Climate possibly plays an important role in the considerably high prevalence of FRS cases in India, Sudan, and Pakistan [10]. Patro et al. recently demonstrated a significant decrease in SNOT-20 and Lund Mackay scores, reduction in polyp size, fungal burden and opacification in AFRS patients who were given preoperative itraconazole for a month [11]. The administration of itraconazole even decreases the need of steroid. Similarly, Seiberling and Wormald et al. showed good response in 83% of patients using oral itraconazole 100 mg BD for 6 months after FESS [12]. Kupferberg et al. noted improved endoscopic scoring when oral antifungals were administered to AFRS
patients while decreased recurrence (around 50%) and revision surgery (around 20%) were reported by Rains and Mineck using oral itraconazole [13].

**Allergic bronchopulmonary aspergillosis (ABPA):** The burden of ABPA in India ranges from 0.12-6.09 million (best estimate, 1.38 [range, 0.86-1.52] million). [14] Two randomized trials evaluating itraconazole in ABPA have shown benefit of itraconazole over placebo. [15,16]. It is suggested to use itraconazole alone in acute exacerbations of ABPA although data regarding this is scarce [16,17]. Studies suggest that itraconazole can improve symptoms in ABPA, decrease the immunological severity (IgE levels and total eosinophil counts), glucocorticoid requirement and the number of acute ABPA exacerbations. Also, oral itraconazole has been found to improve the quality of life in the steroid-dependent asthma patients. [18] Newer azoles including voriconazole and posaconazole are also possibly efficacious in ABPA [19,20,21].

**Phaeohyphomycosis:** Both subcutaneous and systemic phaeohyphomycosis (both cerebral and pulmonary) are reported from different centres in Asia. Although there are no standardized therapies for these patients, the maximum in-vitro activity of these group of fungi against voriconazole and itraconazole has made these antifungal the preferred agents to treat this condition. [22] While oral itraconazole qualifies as the drug of choice due to the extensive clinical experience with it, voriconazole demonstrates superiority for central nervous system infections as it achieves good levels in the cerebrospinal fluid.

**Chromoblastomycosis:** Chromoblastomycosis, a neglected tropical disease has high prevalence in Asian countries with majority of reports from India and China. [23]) The disease is recalcitrant and difficult to treat due to under diagnosis in early course. Itraconazole is the drug frequently used to treat the disease with cure rates ranging from 15-80%. [23]

**Endemic mycoses:** Histoplasmosis occurs in different pockets within India, China and South East Asian countries [24]. The milder disease is managed by itraconazole while severe disease is initially managed liposomal amphotericin B followed by itraconazole. Blastomycosis which is only reported from India among Asian countries is similarly managed. [24] Penicilliosis, also endemic in South East Asia region responds well to itraconazole. The highly prevalent sporotrichosis in Asian region is also treated effectively with itraconazole. [24]
**Candidemia**: Singhi et al noticed oral itraconazole to be effective in treatment of candidemia in children in a pediatric ICU (PICU). [25] Mondal et al also compared itraconazole with fluconazole in pediatric nosocomial candidiasis and found it to be as effective as fluconazole and that too devoid of serious side effects. [26]

**Other fungal infections**: *Fusarium* species are frequent agents of onychomycosis and fungal keratitis, and occasional agents of invasive disease. The drug of choice for the treatment of invasive fusariosis is voriconazole. [27] In addition, recently treatment of dermatophytosis is becoming difficult in Indian scenario. Many patients treated with terbinafine, which was very effective in treatment of this condition is coming back to the hospital with relapse or recurrent infection. The in-vitro data has revealed resistance to terbinafine in some of the strains isolated form those patients and good in-vitro activity to itraconazole.

9. **Reviews of harms and toxicity: summary of evidence on safety**
   As per the document submitted by David Denning

10. **Summary of regulatory status of the medicine**
    As per the document submitted by David Denning


   - http://www.drugs.com/pro/itraconazole.html
   - https://online.epocrates.com
   - https://www.drugs.com/pro/voriconazole.html


