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

Yes, the application gives in-depth analyses of the issues related to public health with respect to many of the fungal infections. Skin infections caused by fungi are the 5th commonest cause of human disease and affect over 900 million people. Dermatophytes, Candida and Malassezia are the commonest causative fungi inflicting both healthy and immunocompromised patients.

A large proportion of these fungal infections occur in people living with HIV/AIDS as part of opportunistic infections.

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

Yes, the authors of the review have given most of the important studies. They have sought the help of a combination of clinical guidelines and RCTs and other supportive data. The application encompasses many trials related to itraconazole.

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

Yes, the discussion under public health relevance represents the various clinical indications of itraconazole.

The overall effectiveness of itraconazole in various clinical trials is described in terms of response rates in specific fungal infections. More than 90% response rates were observed in vulvovaginal candidiasis, oropharyngeal candidiasis, fingernail onychomycosis, blastomycosis, sporotrichosis, non-meningeal coccidioidomycosis, paracoccidioidomycosis and Talaromyces marneffei infection.

The application also enlists the guidelines recommended by the various International agencies for the usage of itraconazole.

However itraconazole is not significantly superior to fluconazole (which is already on the EML) for most of the listed conditions. Hence there is no real need in terms of common indications or priority health care necessities to warrant adding another antifungal agent.

(4) Is there evidence of efficacy in diverse settings and/or populations?

Yes.
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, the application discusses about the various adverse events caused by itraconazole under three heads, viz., immediate, short term and long term adverse events. The frequencies of the individual adverse events are also described in the Table 5.

As described in the application, doses of >400 mg daily (orally) are more commonly associated with adverse events. The most common are of GIT related such as, abdominal pain, nausea, vomiting, diarrhoea and constipation. The next common adverse events are of deranged liver function including increased alanine transaminase, aspartate transaminase, alkaline phosphatase, bilirubin and lactate dehydrogenase.

Itraconazole should not be administered in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF [“Boxed Warning” (US-FDA)]. Cardiac failure is a serious adverse event, though rare, which can be encountered. At times, itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death.

Alopecia (especially in females), can be severe at times with the usage of itraconazole.

ADDITIONAL CONSIDERATIONS:

Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Itraconazole is implicated in various drug-drug interactions and is known to suppress CYP3A4. Itraconazole metabolism is accelerated by concomitant administration of rifampicin, phenytoin and carbamazepine. Action of benzodiazepines, digoxin, cyclosporine, tacrolimus, sirolimus, statins and warfarin can be prolonged by itraconazole. Health care workers should take a careful drug history from the patient before prescribing this medicine. Therapeutic drug monitoring (TDM) is advised for those patients who are co-prescribed with anti-retrovirals (like efavirenz) and/ or rifampicin.

Patients with impaired hepatic function receiving itraconazole require careful monitoring, as itraconazole is predominantly metabolized by liver. Commonly prescribed medicines such as antacids, proton pump inhibitors and H2 blocker reduce the absorption of itraconazole capsules.

Hence use of this medicine in patients with co-morbidities requires careful therapeutic decision making.

Are there any issues regarding the registration of the medicine by regulatory authorities?

From the data accessed from the Orange book of US-FDA, it is clear that the capsule, oral solution, tablet formulations of itraconazole got approval in the years
1992, 1997 and 2010, respectively. It is available in the U.K. and is approved for use in India.

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

Yes, itraconazole is already recommended as a first line treatment in the 2014 WHO Guidelines on skin and oral HIV-associated conditions in children and adults for eosinophilic folliculitis and as second line therapy for tinea (dermatophyte infections).

(9) **Please comment briefly on issues regarding cost and affordability of this medicine.**

Based on the various cost-effectiveness analyses, where indicated, it is found that itraconazole is more cost-effective than griseofulvin but when compared to terbinafine, itraconazole was found to be costlier. Itraconazole is costlier than fluconazole which is already listed in the EML.

(10) **Any additional comments?**

Table 5 is a mere duplication of Table 2, both enlisting adverse effects of itraconazole. The review does not adequately compare itraconazole with the other antifungal agents already in the EML. In the 2013 EML, fluconazole is present with a square box symbol stating that it is representative of a class.

(11) **Please summarise the action you propose the Expert Committee takes.**

I do not support that the committee should add itraconazole in the EML, as there are two other azoles [clotrimoxazole (for topical use) and fluconazole (for systemic use)] in this group which are already in the list. This drug is advantageous over fluconazole only in a very small subset of patients, as mentioned in section No.8 and therefore will not be needed for the majority of patients.