# Itraconazole

Section: 6. Anti-infective medicines > 6.3. Antifungal medicines

EMLc | ATC codes: J02AC02

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| **Indication** | Histoplasmosis ICD11 code: 1F2A.Z |
| **INN** | Itraconazole |
| **Medicine type** | Chemical agent |
| **List type** | Core |
| **Additional notes** | *for treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by T. marneffei and chromoblastomycosis; for prophylaxis of histoplasmosis and infections caused by T. marneffei in AIDS patients |
| **Formulations** | **Oral > Liquid:** 10 mg per mL<br>**Oral > Solid:** 100 mg |
| **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** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Wikipedia** | Itraconazole |
| **DrugBank** | Itraconazole |

## Expert Committee recommendation

The Expert Committee recommended the addition of itraconazole to the EML and the EMLc for treatment of chronic cavitary pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, infections caused by Talaromyces marneffei and chromoblastomycosis, and for prophylaxis of histoplasmosis and infections caused by T. marneffei in AIDS patients. The Committee did not recommend the inclusion of the indication of acute invasive aspergillosis for itraconazole, noting that voriconazole is the current treatment of choice. The Committee recommended that, with the addition of new azoles (itraconazole and voriconazole) to the Model Lists, the square box should be removed from the current listing for fluconazole.

## Background

Itraconazole was considered for inclusion on the EML and EMLc by the Expert Committee in 2015 and was not recommended. The Committee considered that itraconazole could be interpreted to be an eligible alternative agent within the existing square box listing of fluconazole. The Expert Committee accepted the role of itraconazole in the treatment of a wide range of fungal infections, including some for which fluconazole is ineffective, such as aspergillosis. The Committee noted that itraconazole demonstrated similar efficacy to fluconazole for many indications but is inferior to other antifungal agents in other settings (e.g. induction and maintenance therapy for cryptococcal meningitis). Further, the Committee noted that the capsule and oral solution formulations were not

interchangeable and dosing recommendations differed in relation to food. The Committee also noted the large number of significant drug–drug interactions associated with itraconazole and the use of therapeutic drug monitoring for those with life-threatening infections (1).

## Public health relevance

Chronic pulmonary aspergillosis (CPA) is estimated to affect more than 3 million people worldwide, of whom approximately 1.2 million have had tuberculosis (2). Following pulmonary tuberculosis, 25¬–33% of patients are left with residual cavitation in the lung and, of these, 10–35% develop CPA. Five-year survival without antifungal treatment is approximately 20% (3, 4). It is estimated that more than 200 000 people develop acute invasive aspergillosis annually (5). The disease is common in people with acute leukaemia, those who have haematopoietic stem cell transplantation (HSCT) and other transplant recipients (6). Less commonly, invasive aspergillosis occurs in people receiving corticosteroids for many reasons including chronic obstructive pulmonary disease (>1.2% of admissions to hospital), lung cancer and autoimmune disorders (such as systemic lupus erythematosus) (7). Other significant risk factors include medical intensive care, liver failure and severe burns (8). However, as some of these conditions are more prevalent than haematological cancer and transplantations, the number of individuals with invasive aspergillosis may be higher than estimated. Mortality without antifungal treatment is 100%. Disseminated histoplasmosis is the most common opportunistic infection of newly presenting AIDS patients in parts of Latin America and is a fatal infection if untreated (9). Other at-risk groups include those at the extremes of age and the immunosuppressed. Chronic cavitary histoplasmosis is a rare complication of histoplasmosis for which patients with chronic obstructive pulmonary disease are at risk (10). Sporotrichosis has been reported worldwide but most cases occur in central and south America and China (11, 12) with rates of 1 case per 1000 in hyperendemic rural areas. The infecting fungus, Sporothrix schenckii, usually enters the body by traumatic implantation. Disease may become disseminated in patients with AIDS. Paracoccidioidomycosis is endemic to Latin America; there are estimated to be fewer than 10 000 cases worldwide annually (13). Risk of more severe infection is associated with AIDS and smoking. There is a high rate of coinfection with tuberculosis (11, 14). Systemic mycoses due to T. marneffei infection in patients with AIDS present all over the world. It has been estimated that approximately 10% of AIDS patients in China, Hong Kong Special Administrative Region, and around 30% of AIDS patients in northern Thailand are affected (15). The infection is known to affect other immunocompromised patients and is potentially fatal if untreated (16). Chromoblastomycosis is characterized by proliferating, chronic, disfiguring skin lesions. The highest prevalence of the disease is in tropical and subtropical climates. Incidence rates up to 14/100 000 have been reported.

## Benefits

The application presented the outcomes of various prospective studies of itraconazole by indication (refer to Tables 3 to 9 of the application). Chronic pulmonary aspergillosis (17–19) A small randomized controlled trial (RCT) compared itraconazole with supportive therapy in 31 patients with chronic cavitary pulmonary aspergillosis (18). Response to therapy was assessed clinically, radiologically and overall following 6 months of therapy. Overall response was 76.5% in the itraconazole group versus 35.7% in the standard care group. The difference was statistically significant (P = 0.02). The percentage of patients showing clinical and radiological response were also higher in the itraconazole group. Acute invasive aspergillosis (20, 21) A multicentre prospective, uncontrolled study investigated oral itraconazole in 76 evaluable patients with various underlying conditions (21). Response was assessed on the basis of clinical and radiological criteria and categorized as complete, partial or stable. Treatment duration varied from 0.3 to 97 weeks. At the end of treatment, complete/partial or stable responses were observed in 39% and 4% of patients, respectively. Therapy was discontinued in 26% of patients because of clinical worsening or death due to aspergillosis; 30% of patients withdrew for other reasons (toxicity, death from other causes). Itraconazole failure rates varied widely according to site of disease and underlying disease group and were as high as 44% in AIDS patients. Histoplasmosis Two studies evaluated itraconazole for treatment of histoplasmosis (22, 23). Treatment success was observed in over 80% of patients in both studies. In an RCT of itraconazole versus placebo for prophylaxis, histoplasmosis developed in 2.7% of patients in the itraconazole group versus 6.8% of patients given placebo (P = 0.03) (24). In general, 19.5% of patients in the itraconazole

group developed a fungal opportunistic infection compared with 28.8% in the placebo group (P = 0.004). Prophylaxis significantly reduced the incidence of histoplasmosis (P = 0.02; log-rank test) and all invasive fungal infections (P = 0.0009; log-rank test) in patients with CD4 counts <100/mm3. Sporotrichosis Three prospective, uncontrolled multi-centre studies evaluated itraconazole in patients with cutaneous, systemic and lymphangitic sporotrichosis (25–27). High or complete response to itraconazole was reported in all three studies. Paracoccidioidomycosis A retrospective cohort study compared itraconazole with sulfamethoxazole + trimethoprim (SMX-TMP) in 200 patients with mild or moderate paracoccidioidomycosis (28). There was a higher incidence of response with itraconazole than with SMX-TMP, with cure rates of 86.4% and 51.3%, respectively. In addition, the median treatment period for itraconazole was significantly shorter than for SMX-TMP: 12 months and 23 months, respectively. A Cox proportional hazard regression model showed that use of itraconazole increased the hazard of cure compared with the use of the SMX–TMP. Mycoses caused by T. marneffei In a prospective, uncontrolled trial in 74 HIV-infected patients with disseminated T. marneffei infection, treatment with IV amphotericin B for 2 weeks, followed by 10 weeks of oral itraconazole was associated with a 97.3% response to treatment (29). Itraconazole for primary prophylaxis was compared with placebo in an RCT of 129 patients infected with HIV (30). Results from the intent-to-treat analysis showed development of systemic fungal infection (T. marneffei) in 1.6% of the itraconazole group and in 16.7% receiving placebo (cryptococcal meningitis (n = 7), T. marneffei (n = 4); P = 0.003)). Chromoblastomycosis Two prospective, uncontrolled studies evaluated the effectiveness of itraconazole in a small number of patients with chromoblastomycosis infection due to Fonsecaea pedrosoi (31, 32). At a dose of 200–400 mg/day itraconazole, 42% of patients with mild to moderate disease achieved a clinical and biological cure after a mean therapy duration of 7.2 months (3.2–29.6 months). Clinical improvement was observed in 21% of patients with severe lesions after a mean 17.6 months of treatment (10.7–22.5 months). In total, 12 (63%) of 19 patients benefited from itraconazole treatment (31). In a small study of 10 patients given 100–200 mg/day itraconazole, 90% of patients showed benefit (cure, major improvement or minor improvement) after 12 months of treatment (32). Itraconazole is included as a recommended (or alternative) treatment for the proposed infections in international guidelines (33–36).

## Harms

Known adverse events associated with itraconazole include gastrointestinal effects, hepatic dysfunction, QT-interval prolongation, rash, metabolic disturbances and cardiovascular events including hypotension, congestive cardiac failure and peripheral oedema. Dose adjustment may be necessary in the presence of renal impairment, and patients with hepatic impairment or taking other hepatotoxic medicines require careful monitoring (37). Itraconazole is associated with a number of drug–drug interactions occurring via several different mechanisms: medicines that inhibit gastric acid secretion, such as antacids, proton-pump inhibitors and H2-antagonists, all reduce absorption of itraconazole capsules. Itraconazole metabolism is accelerated by concomitant administration of rifampicin, phenytoin and carbamazepine, which may mean that therapeutic serum concentrations cannot be achieved (38). In addition, many clinically significant interactions relate to the suppression of CYP3A4 (cytochrome P450 3A4) activity by itraconazole, which leads to higher exposures to agents that are metabolized via this route. Itraconazole also prolongs the action of midazolam, digoxin, ciclosporin, tacrolimus, sirolimus, statins and warfarin (39–42). There are also clinically important interactions between itraconazole and many antiretroviral medicines.

## Additional evidence

Differences in bioavailability between itraconazole capsules and oral liquid are considerable and the two formulations are not interchangeable. Itraconazole oral liquid has better oral bioavailability than itraconazole capsules and produces approximately 30% higher systemic drug exposure (43). Oral bioavailability of itraconazole capsules is affected by the presence of food, which is not the case with itraconazole oral liquid.

## Cost / cost effectiveness

The mean daily treatment cost for 400 mg itraconazole was estimated at US$ 6.73. Costs were estimated in the application to range from less than US$ 0.01 in Sri Lanka and Zambia to US$ 102 in Sweden.

## WHO guidelines

N/A

## Availability

Widely available, including generics.

## Other considerations

The Expert Committee considered that therapeutic drug monitoring (TDM), where available, may help inform management considerations, especially with regard to preventing underdosing. In severe infections, however, the Committee felt that the clinical benefits of unmonitored therapy would often outweigh the benefits of additional TDM and thus considered that core listing (as opposed to complementary listing) was appropriate.


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