20th Expert Committee on the Selection and Use of Essential Medicines

April 2015

The 20th Expert Committee meeting will take place at WHO Headquarters, Geneva, in April 2015 in order to revise and update the WHO Model List of Essential Medicines for both adults and children. Applications for inclusion, change (addition or modification of an indication) or deletion of a medicine in the next WHO Model List of Essential Medicines 2015 should be sent in the recommended electronic format (both a pdf file and a Word document) to the WHO Essential Medicines List Secretariat between 15th June and 1st December 2014 (email: emlsecretariat@who.int).

APPLICATION TO ADD ITRACONAZOLE TO THE ESSENTIAL LIST OF MEDICINES FOR TREATMENT OF FUNGAL DISEASES

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2. Summary statement of the proposal for inclusion, change or deletion

Currently, the WHO list of essential medicines only includes one topical azole drug, cotrimoxazole and one systemic azole, fluconazole. Oral and intravenous azole drugs are basic treatments for many fungal diseases - cutaneous, mucosal, chronic, allergic and invasive. While fluconazole is active against yeast infections and is on the EML, it has no activity against *Aspergillus* spp. and is inferior to itraconazole for many indications. Itraconazole, currently available as generic drug in most countries is the agent of choice for histoplasmosis, sporotrichosis, blastomycosis, paracoccidioidomycosis, chromoblastomycosis, allergic bronchopulmonary aspergillosis, eosinophilic folliculitis in AIDS and an agent of choice for onychomycosis, vulvovaginal candidiasis, chronic pulmonary aspergillosis, coccidioidomycosis and many cutaneous fungal infections. For middle and low-income countries itraconazole has some specific therapeutic merits - the prophylaxis of fungal infections in neutropenia, invasive aspergillosis and some HIV patients needing azole maintenance therapy after cryptococcal meningitis living in *Histoplasma* or *Talaromyces* endemic. Multiple generic capsule forms of itraconazole are available; oral solution and intravenous drug are still branded products. Itraconazole has a tolerable toxicity profile, but numerous drug/drug interactions requiring care in prescribing, notably with some anti-retrovirals (ARVs) and rifampicin. Most high-income countries undertake therapeutic drug monitoring of itraconazole serum/plasma levels for patients receiving itraconazole for life-threatening infection and long-term therapy.

This application recommends inclusion of oral itraconazole capsules 100mg, itraconazole oral suspension 10mg/mL and intravenous formulation 10mg/mL onto both the adult and paediatric EML.

3. Name of the focal point in WHO submitting or supporting the application

(where relevant)

- Dr Nicola Magrini

4. Name of the organization(s) consulted and/or supporting the application

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5. International Non-proprietary Name (INN, generic name) of the medicine

- Itraconazole

6. Formulation proposed for inclusion; including adult and paediatric

(if appropriate)

- Capsules 100mg
- Oral suspension 10mg/mL
- Intravenous formulation 10mg/ml

7. International availability - sources

if possible manufacturers and trade names

Figure 1. Map showing countries where itraconazole is available. For more detail see www.gaffi.org/why/burden-of-disease-maps/

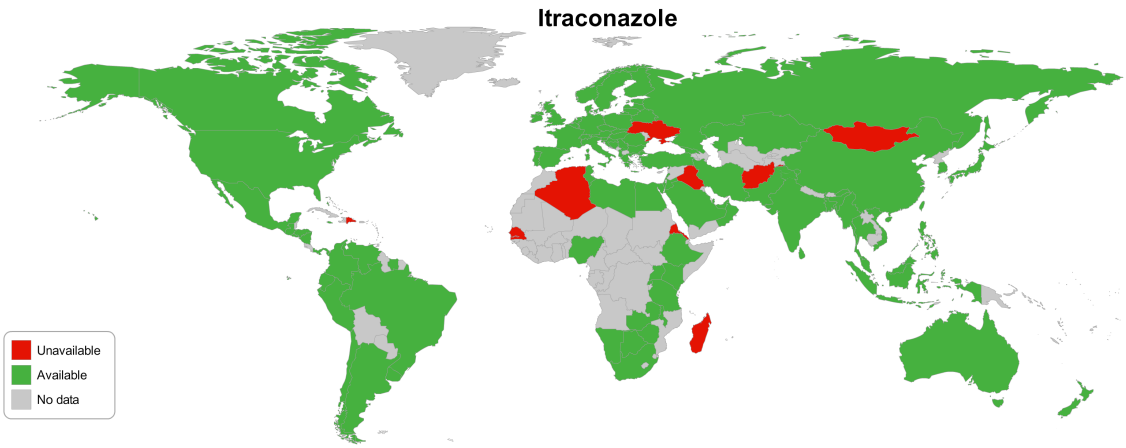
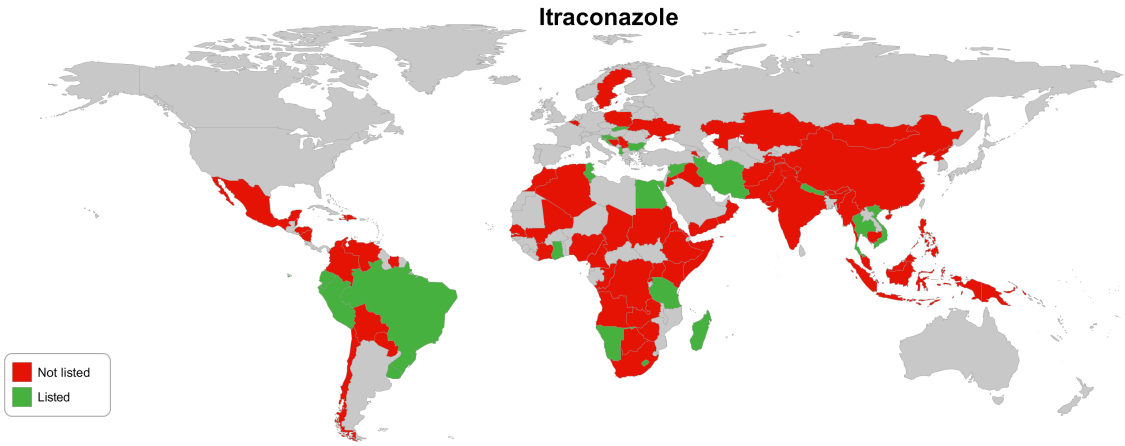


Figure 2. Map showing where itraconazole is listed on countries essential medicines list. For more detail see www.gaffi.org/why/burden-of-disease-maps/



Janssen Pharmaceutica (Johnson and Johnson) and affiliates sell Sporanox all over the world, in all three formulations. Sandoz sell generic capsules in Europe, Ecuador, Jamaica, Panama, South Africa, Taiwan, Trinidad and Tobago, USA and Venezuela. Multiple other generic manufacturers produce itraconazole capsules: in India they include Biospore (Biosciences), Candistat Cap (Merck), Canditral (Glenmark), Fulcover (Saga Lab), Fungicap (PIL), Itaspor (Intas), Itra (East West),

Itrazen (Kaizen Pharma), Itrole (Chemo) and Itzucia (United Biotech). An enhanced absorption formulation (Lozanoc – Mayne Pharma) is also available in China, South Korea and Europe.

8. Whether listing is requested as an individual medicine or as an example of a therapeutic group

- Individual medicine under EML section **6.3 Antifungal medicines.**

9. Information supporting the public health relevance

(epidemiological information on disease burden, assessment on current use, target population)

The information provided in this section encompasses the clinical use of itraconazole.

9.1. Vulvovaginal candidiasis

Thrush is common. About 70% of all premenopausal women develop thrush at some point in their lives (1). By a mean age of 24 years, 60% of women had suffered at least one episode of vulvovaginal candidiasis and 36% had at least one episode a year and 3% had it 'almost all the time'. Estimates suggest 88-158 million (5–9%) women get 4 or more attacks of vulvovaginal candidosis annually across the world. In these patients there is often a worse response to initial treatment and a shorter time to relapse (1-3). There are no estimates of the frequency of chronic vulvovaginal candidiasis (cVVC), but is less common than recurrent vulvovaginal candidiasis (rVVC). There is a rising frequency of infections due to fluconazole unresponsive species such as *Candida glabrata (*4).

Underlying problems and at risk patients include pregnancy, antibiotic use, diabetes mellitus and cystic fibrosis. HIV-seropositive women are not more likely to develop vaginal candidiasis than controls (5). Oestrogen status is important, accounting for post-menopausal women having rVVC on hormone replacement therapy (HRT)(6). Other risk factors such as corticosteroid use and frequent antibiotic use should be identified. If sporadic risk factors can be identified

prophylactic antifungal treatment can be used at the time. In many cases, however, the risk factors are persistent or cannot be identified (7).

9.2. Oropharyngeal candidiasis

Oral thrush in HIV/AIDS occurs in ~9.5 million people worldwide based on ~90% of patients not taking but needing anti-retroviral therapy (8). At least another 1-4 million are affected who do not have HIV infection.

Underlying problems and at risk patients are those with HIV/AIDS, with declining immunity as well as in leukaemia and following stem cell transplantation unless prevented with antifungals. It is also common in newborns and patients on head and neck radiotherapy (9, 10). Occasionally it affects asthmatics taking inhaled steroids and other immunocompromised patients, such as those with chronic mucocutaneous candidiasis (rare genetic disorder) caused by either the AIRE mutation or a STAT1 mutation, and those with CARD9 immunodeficiency (11, 12). Fluconazole is the most prescribed azole agent for this indication, but itraconazole solution is effective in those with fluconazole resistant oral candidiasis (8).

9.3. Oesophageal candidiasis

Candida oesophagitis affects an estimated ~2 million people as ~20% of HIV/AIDS patients not on anti-retroviral therapy, and ~0.5% if on antiretroviral therapy develop it. Other patients might increase the numbers by 10-20% (13). The risk in HIV infection and AIDS is greatest when the CD4 count is below 100 x 10_6/l. Cancer and neutropenic patients are at risk. There are rare reports of oesophageal candidiasis in immunocompetent individuals after omeprazole therapy, suggesting that hypochlorhydria favours colonization. Chronic mucocutaneous candidiasis involves the oesophagus. Fluconazole is the most prescribed azole agent for this indication, but itraconazole solution is effective in those with fluconazole resistant oesophageal candidiasis (14).

9.4. Skin Infections

Skin infections caused by fungi are the 5th commonest cause of human disease and affect over 900 million people in the most recent estimate of the global burden of disease (15). While *Candida* infections can involve skin surfaces in both healthy and

immunocompromised patients the commonest skin infections are those caused by dermatophyte or ringworm fungi and *Malassezia*, a yeast which can cause a widespread superficial infection (16-19). The dermatophytes, in particular, cause a significant burden of illness in children with some countries of sub-Saharan Africa seeing prevalence rates as high as 35% in school children (20-22). *Malassezia* infections are also seen in both healthy and immunocompromised patients and are reported widely in those with HIV/AIDS. Immunological reactions to this fungus leading to skin disease are also prevalent in HIV (16). Eosinophilic folliculitis, which presents with intolerable itching is a common example seen in African settings (16).

9.5. Prophylaxis against fungal infection during neutropenia due to haematological malignancy, aplastic anaemia and myelodysplasia

Neutropenic patients have high rates of both mucosal candidiasis and invasive aspergillosis. Prior to the routine use of either/or antifungal prophylaxis and empirical antifungal therapy, ~25% of patients would develop a fatal invasive fungal infection, rising to 70% in those neutropenic for 30 days or more. Itraconazole solution is very effective in the prevention of mucosal candidiasis and partially effective in preventing invasive aspergillosis.

9.6. Acute invasive aspergillosis

Over 30 million people are at risk of invasive aspergillosis each year because of corticosteroid or other therapies, and over 200,000 patients develop it annually (13). The disease is common in people with acute leukaemia, stem cell and other transplants (especially lung). Less commonly, invasive aspergillosis occurs in people receiving corticosteroids for many reasons including chronic obstructive pulmonary disease (>1.2% of admissions to hospital) and autoimmune disorders (such as systemic lupus erythematosus) (23). Other significant risk factors include medical intensive care (immunoparalysis following bacterial infection) (1.1-5.8%), liver failure and severe burns (24). However, as some of these conditions are more prevalent than haematological cancer and transplanted patients, the number of individuals with invasive aspergillosis is probably twice as high as estimated.

9.7. Chronic pulmonary aspergillosis

Chronic pulmonary aspergillosis is a worldwide problem, estimated to affect over three million people worldwide, of whom ~1.2 million have had tuberculosis (25). Following pulmonary tuberculosis, 25-33% are left with residual cavitation in the lung and of these 10-35% develop chronic pulmonary aspergillosis. Unpublished data indicates an even higher frequency of the key marker of chronic pulmonary aspergillosis (*Aspergillus* antibody) in smear negative tuberculosis, including HIV positive patients. Underlying problems and at risk patients include pulmonary tuberculosis, chronic obstructive pulmonary disease, sarcoidosis, allergic bronchopulmonary aspergillosis, prior pneumothorax, prior lung cancer (sometimes with lung radiotherapy or surgery) and asthma (including severe asthma with fungal sensitization (SAFS)) (25). Most patients are not taking corticosteroids or other immunosuppressant drugs and are not considered immunocompromised (26).

9.8. Allergic bronchopulmonary aspergillosis (ABPA)

ABPA is seen worldwide affecting asthmatics and those with cystic fibrosis. ABPA is uncommon in childhood. Frequency estimates vary from 0.7 to 4.1% of consecutive asthma patients referred to a chest specialist, which suggests about 4.8 million affected, amongst the ~200 million adults with asthma. ABPA tends to be found in the worst affected asthmatics, and may be associated with status asthmaticus. About 12-15% of adolescent and adult cystic fibrosis patients are affected (27, 28).

9.9. Blastomycosis

Blastomycosis caused by *Blastomyces dermatitidis,* is endemic to North America and has been noted occasionally in Africa and India (29). Studies performed in the USA showed that the incidence of this infection is between 0.5-7 per 100,000 people. Contact rates with the fungus are probably much higher. Most affected patients are healthy adults, particularly middle aged men undertaking sports or work in rural or wild areas. Immunocompromised patients are at increased risk of severe disease (30).

9.10. Sporotrichosis

Sporotrichosis caused by *Sporothrix schenckii,* has been reported worldwide with most reported cases from Central and South America (Mexico, Colombia, Brazil, Peru and part of China) (31, 32). Hyperendemic rural areas may have attack rates of 1 case per 1000 of the population. In northern India, ~30% of inhabitants in villages where sporotrichosis had been reported had evidence of exposure to the organism compared with 6% in villages without clinical cases. Occasionally point source outbreaks occur, related to infected cats, moss used for planting and hay. Those at risk patients include farmers, gardeners and forestry workers (32). Those affected are usually healthy adults under the age of 30 but young children may also be infected. *S. schenckii* most commonly enters the body through traumatic implantation but a minority of patients do not recall any history of trauma. AIDS may lead to disseminated sporotrichosis (33).

9.11. Histoplasmosis

Histoplasmosis is caused by *Histoplasma capsulatum.*

9.11.1. Histoplasmosis acute pulmonary

Exposure is common in the areas in which histoplasmosis is endemic. However symptomatic disease is uncommon. Those at risk include cavers (spelunkers) and those in the construction industry, doing excavation or demolishing or building new buildings, cleaning chicken coops and heavy outdoor work (34). The organism thrives in bat and bird guano. The larger the inoculum, the more severe the illness is. Primary infection in immunocompromised patients, especially those with advanced HIV infection and taking corticosteroids can be severe and fatal (31).

9.11.2. Disseminated histoplasmosis

In some localities in Latin America, disseminated histoplasmosis is the most common opportunistic infection of newly presenting AIDS patients, and occurs throughout the world at a lower frequency (30, 35, 36). Some patients present in shock, requiring intensive care, most have less severe manifestations. Other risk groups include those at extremes of age and immunosuppression for other reasons (37).

9.11.3. Chronic cavitary Histoplasmosis

Chronic cavitary pulmonary histoplasmosis is an unusual or rare complication of histoplasmosis. At risk patients include patients with chronic pulmonary disease, especially COPD is typical for chronic cavitary pulmonary histoplasmosis (36).

9.12. Coccidioidomycosis

Coccidioidomycosis caused by *Coccidioides immitis* and *Coccidioides posadasii*, is restricted to the Americas. An estimated 150,000 infections occur annually in the USA, and an unknown number in central and South America (38). Approximately 25,000 new, clinical cases of coccidioidomycosis are reported annually in the USA leading to ~75 deaths per year. Occasional epidemics occur. Case numbers have been rising in Arizona, possibly related to immigration to the state and building on previously wild desert areas, with 7 cases per 100,000 persons in 1990, increasing ~75 cases per 100,000 persons in 2007 (39, 40). The most affected countries outside the USA are Mexico, Guatemala, Brazil, Paraguay and Argentina (31).

Most patients with coccidioidomycosis are previously healthy. Dissemination is more common in certain racial groups including Filipinos and African-Americans, as well as men. Pregnancy (second or third trimester) increases the risk of dissemination. Immunocompromised patients, especially those on corticosteroids or with advanced HIV infection or AIDS, are at particular risk of dissemination. Coccidioidal meningitis is a particularly devastating complication, affecting about 0.5% after primary infection and requiring life long antifungal therapy (39).

9.13. Paracoccidioidomycosis

Paracoccidioidomycosis causes by *Paracoccidioides brasiliensis*, is endemic to all Latin America, especially Brazil. The largest number of cases has been reported in Brazil, Venezuela, Argentina, Uruguay, Ecuador, Colombia, Peru and Paraguay. Relatively few cases are reported from Bolivia or French Guiana. In Brazil there are probably ~ 3,500 annually, so <10,000 worldwide (41). The incidence may be declining because of changing agricultural practices and greater urbanization. Males are affected much more frequently than females, although a similar sex frequency is seen in pre-pubertal girls and post-menopausal women. Oestrogen blocks the mould to yeast transition in the fungus, preventing infection. AIDS

increases the risk of more severe infection. Smoking probably increases the risk of chronic pulmonary disease. Many patients with pulmonary paracoccidioidomycosis also have tuberculosis (31, 37).

9.14. Systemic Mycoses due to *Talaromyces marneffei* infection

(former name Penicilliosis)

Systemic Mycoses caused by *Talaromyces marneffei* (former known as Penicilliosis), a genus shift very recently made from *Penicillium marneffei,* originate from Southeast Asia, notably Thailand, Vietnam, Hong Kong, southern China, Taiwan, India, Indonesia, Cambodia and Laos, unless laboratory acquired (42-45). About 10% of AIDS patients in Hong Kong and ~30% of patients in N. Thailand present with *T. marneffei* infections (46). Patient with AIDS and penicilliosis present all over the world, following travel. Almost all patients present with have HIV infection, with CD4+ counts <100 $x10^6$/L. It rarely occurs in other immunocompromised patients (47).

9.15. Chromoblastomycosis

It is a cutaneous and subcutaneous mycosis characterized by the appearance of proliferating chronic skin lesions following traumatic implantation of the fungus. Sites most commonly affected are the lower limbs. Upper limbs and buttocks are also frequently involved. Ear, face, neck and breasts have been reported sporadically. Lesions start as nodule or papule that slowly enlarge becoming verrucose and wart-like. Old lesions can be tumorous or cauliflower-like in appearance. Lymphatic and haematogenous dissemination have been described but they are infrequent. Many melanised (black fungi) fungal species can be the etiologic agents of this disease. The most frequent are: *Fonsecaea pedrosoi and Cladophialophora carrionii*. The highest prevalence of the disease is within a zone between 30° latitude North and 30° latitude South, coinciding with most of the tropical and subtropical climates. Chromo has no compulsory notification and so all epidemiology data is derived from published case reports and surveys. Incidence rates range from 1:6,800 (14/100,000) (Madagascar) to 1/ 8,625,000

(0.012/100,000) (USA). In Brazil the estimate incidence rate for this disease is 3/100,000 (37).

Most of the reported cases occur in Latin America, the Caribbean, Asia, Africa and Australia. Madagascar, Brazil, Mexico, Dominican Republic, Venezuela, India and Southern China contribute with the majority of cases (48-55) .

9.16. Cryptococcal meningitis

An estimated 1 million people develop cryptococcal meningitis worldwide each year, mostly AIDS-related. Cryptococcal meningitis is more common in sub-Saharan Africa and tropical countries (Brazil, Thailand, Malaysia, Papua New Guinea, etc.) (47, 56). In US, active population-based surveillance, conducted between 1992-1994, showed cryptococcosis developed in 2-5% of HIV-infected persons per annum (57). The annual incidence has declined following widespread use of fluconazole and introduction of more effective combination antiretroviral treatment. Among HIV-negative persons in US, average annual incidence has remained almost constant at about 1 case per 100,000 population (58). In China, only 15% of affected patients are HIV infected. In addition to AIDS, transplantation and other immunocompromised patients are at increased risk (59). There is no underlying disease present in some people, especially in the tropics (60).

9.17. Systemic candidiasis

Candidaemia occurs at a population rate of 2-18/100,000, so >300,000 cases are predicted worldwide every year (13, 61-65). Candidaemia comprises about 40% of all patients with invasive candidiasis, including intra-abdominal infection. Underlying problems and at risk patients include prematurity, especially extremely low birth weight infants, chemotherapy and neutropenia, critical care, pancreatitis (17.5% rate), major trauma, burns, multiple antibiotics, renal dialysis or dysfunction, central venous catheterisation (66).

10.Treatment details and guideline

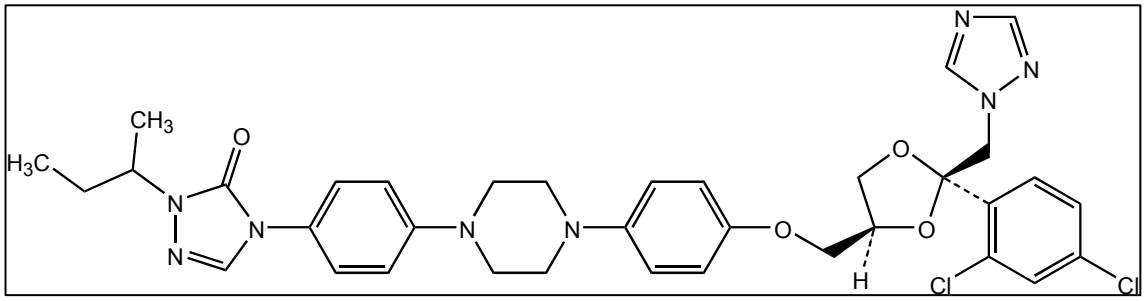
(dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

Itraconazole is a first-line agent for the prevention and treatment of invasive and allergic fungal infections. Itraconazole was initially synthesised in 1980 and has broad spectrum antifungal activity. It was the first orally bioavailable triazole with activity against medically important opportunistic filamentous fungi such as *Aspergillus* spp (67) and is therefore used for the treatment of allergic and invasive aspergillosis, superficial candidiasis, dermatophyte infections, sporotrichosis, blastomycosis, histoplasmosis, penicilliosis and coccidioidomycosis (68-78). Itraconazole is the treatment of choice for most cases of histoplasmosis, sporotrichosis, penicilliosis (*Talaromyces marneffei* infection), chromoblastomycosis and paracoccidioidomycosis, with excellent response rates. 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) (79). It is also recommend in national guidelines for different superficial infections, for instance the UK guidelines for tinea capitis (80). Itraconazole also forms part of the National Institute of Clinical Excellence (NICE) recommendations for superficial mycoses requiring oral therapy (81, 82)

10.1. Structure and Formulations

The structure of itraconazole is shown in the Figure 1.

Figure 1. Structure of itraconazole.



The active site of the molecule (triazole ring) is attached to a side chain that is responsible for the spectrum of antifungal activity, potency and toxicity profile.

Itraconazole is highly lipophilic, poorly soluble at physiological pH and extensively protein-bound in circulation. There are three formulations that are available for clinical use: capsules, an oral solution and an intravenous formulation. The original capsule formulation is manufactured by Janssen and currently marketed as Sporanox. The oral suspension and intravenous formulation, also originally manufactured by Janssen, are both formulated with hydroxypropyl-β-cyclodextrin.

Cyclodextrins are carbohydrate ring structures (or glucose oligomers) produced by the enzymatic degradation of starch (83). β-cyclodextrin is a by-product of starch metabolism produced by *Bacillus macerans* and other bacteria (83). Cyclodextrins form water-soluble complexes with lipophilic agents because they have hydrophobic interiors with hydrophilic exteriors. Cyclodextrins are not necessarily biologically innocuous: they cause osmotic diarrhoea and some cyclodextrins are either nephrotoxic or accumulate with renal impairment (12, 84).

Oral itraconazole suspension has improved oral bioavailability that results in ~30 % higher systemic drug exposure compared with itraconazole capsules (85). Improved oral bioavailability and systemic drug exposure is associated with improved clinical outcomes for patients with oropharyngeal candidiasis (86) and prevention of invasive aspergillosis (87). Intravenous itraconazole is used for the treatment of life threatening systemic mycoses and enables target concentrations of >0.5 mg/L to be achieved in the first 48 hours of treatment (88).

Multiple other generic itraconazole formulations are currently available throughout the world although the pharmacokinetics of these preparations remains largely undefined. Use of generic formulations may not necessarily be bioequivalent, partly because the criteria for bioequivalence adopted by the major regulatory agencies are broad and established in male volunteers, not patients.

10.2. Drug Target, Mechanism of Action and Antifungal Resistance

The triazoles inhibit eukaryotic cytochrome p450 enzymes, a superfamily of haemproteins involved in the synthesis and detoxification of compounds through hydroxylation (89). In fungi, cytochrome p450 enzymes are critical for the biosynthesis of cell membrane sterols. The major target for triazoles, the enzyme 14-α-demethylase is essential (synonyms: P450DM, ERG11, ERG16 and CYP51) is

involved in the progressive removal of methyl groups from lanosterol as part of the biosynthesis of ergosterol. Ergosterol is the predominant sterol in the fungal membrane of most fungi, *Pneumocystis* being a major exception. Triazoles induce a profound disruption in the normal balance of sterols (90, 91) leading to a decrease in ergosterol content and an accumulation in methylated precursors (91). Structural models of Cyp51 in *C. albicans*, *A. fumigatus* and *C. neoformans* show the enzyme's active site to be buried within the core of the protein. The floor of the active site has a haem moiety (92-94). A highly conserved cysteine residue at position 470 forms the axial thilate ligand (92). Additional conserved residues may establish the redox potential of the haem moiety. In addition to the active site that is common to the triazole antifungal class, itraconazole has a comparatively long side chain. The terminal alkyl group of this side chain (see Figure 1) interacts with residues in the substrate access channel that enables the triazole ring to be brought into proximity with haem moiety at the base of the active site. Itraconazole is initially recognised by a hydrophobic patch of amino acids on the protein surface adjacent to the access channel before being partitioned down the channel to the active site with the aid of a series of hydrophobic interactions (92).

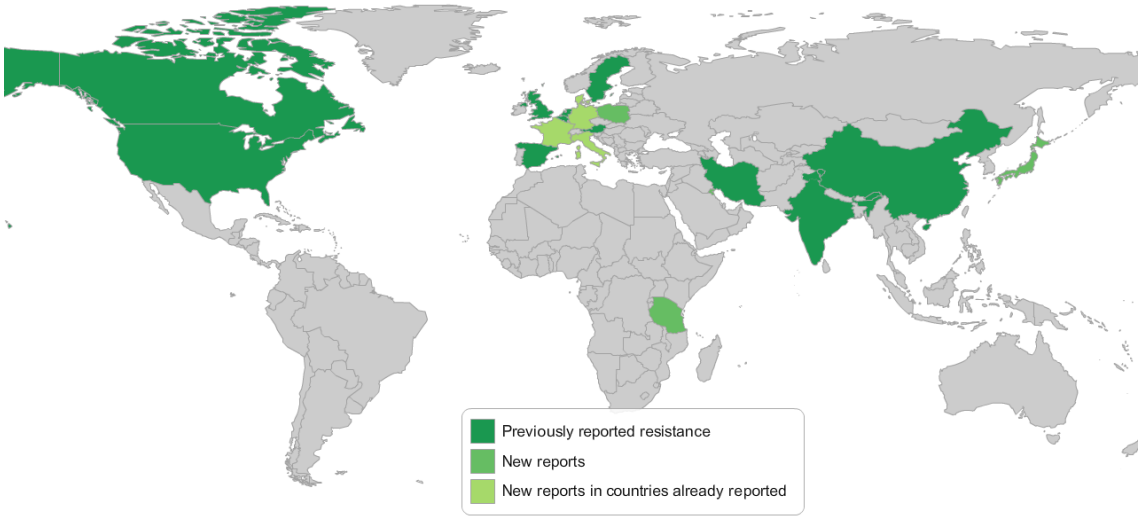
The oxidative demethylation of the natural substrate catalysed by 14-alphademethylase requires NADPH and molecular oxygen. This reaction is also inhibited by carbon monoxide (CO) (95). The nitrogen atom (N4 in triazoles and N3 in the imidazoles) in the heterocyclic ring of the imidazoles and triazoles binds the protohaem iron, which leads to exclusion of the oxygen that is required for the oxidation reaction (96). The degree of enzyme inhibition is likely a function of the strength of binding between the triazole and the enzyme and this is thought to be largely mediated by the side arm that binds to the apoprotein (90). The large side arm group of itraconazole may facilitate close and tight binding between the triazole ring and the haem iron (97). Itraconazole binds to other cellular structures and disrupts other biological processes in the fungal cell, as demonstrated by alternative (non-CYP51A mediated) mechanisms of resistance.

10.3. Mechanisms of resistance to Itraconazole

Most commonly, triazole resistance results from several point mutations in the gene encoding the target protein Cyp51A, sometimes in combination with increased CYP51A copy number. These changes are most studied in *A. fumigatus*. However, a significant proportion of isolates with elevated itraconazole MICs lack CYP51A mutations (98). Other resistance mechanisms such as efflux pumps are described (98). Infection with a triazole-resistant strain may theoretically develop via two potential mechanisms: in vivo selection within individuals with chronic fungal infection who are exposed to triazoles for prolonged periods (months to years); or, primary infection with environmental strains with acquired resistance presumably resulting from widespread use of agricultural azole compounds. The latter appears to be the case especially in the Netherlands and other countries in continental Europe (99). Multiple resistance mechanisms have been documented in isolates from single patients receiving long-term itraconazole (100).

The first cases of itraconazole resistance in *A. fumigatus* were reported in the 1990s and characterised in laboratory animal models of disseminated aspergillosis (101). Until recently, the true incidence of triazole resistance has remained largely undefined because many institutions do not routinely perform susceptibility testing of clinical *Aspergillus* isolates. A rapid screening method has been devised that uses an agar dilution technique (102). A range of molecular assays have been developed that enable the direct detection of resistance from clinical samples (25). Resistant clinical isolates of *A. fumigatus* have now been reported in Europe, the USA, Canada, South America, China, Japan, India and Tanzania (see figure) (25, 99, 102-111). Importantly, many isolates of *Aspergillus fumigatus* demonstrate cross-resistance to other triazoles - this significantly limits therapeutic options and essentially deprives patients of any effective orally bioavailable compounds (112). MIC values for non-*fumigatus* species such as *Aspergillus niger* may be higher than for *Aspergillus fumigatus* (113)—whether this translates to poorer clinical outcomes is not known. Resistance also occurs in *Candida* spp., at a slightly lower frequency than fluconazole, but is extremely rare in dermatophytes and endemic fungi such as *H. capsulatum*.

Figure 3. Map showing countries with itraconazole resistance described as of late 2014.



In vitro susceptibility breakpoints for itraconazole against *Candida* spp. for mucocutaneous disease have been determined by the Clinical and Laboratory Standards Institute (CLSI), and are as follows: susceptible ≤0.125mg/L, susceptible dose-dependent 0.25-0.5 mg/L, and resistant >1mg/L. Breakpoints for itraconazole against *Aspergillus* spp. have not yet been determined by CLSI. Recently, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set breakpoints for itraconazole against *Aspergillus* spp. (113). These breakpoints are based on epidemiologic cut-off values and not supported by extensive pharmacodynamic or clinical data, neither of which is available. The current breakpoints are designed to ensure isolates that have a defined genetic mutation in CYP51 are classified as resistant. Breakpoints using EUCAST susceptibility testing methodology for itraconazole against *Aspergillus fumigatus* are ≤1 mg/L (susceptible), 2 mg/L (intermediate) and >2 mg/L (resistant) (113). The EUCAST MICs for non wild-type isolates vary with the underlying mechanism are generally >4 mg/L for the most commonly identified mutants (alterations at G54, G138, M220, and the environmental phenotype TR-L98H). An in vitro pharmacodynamic study suggests these resistance mechanisms cannot be overcome with dosage escalation and higher systemic drug exposure (114).

10.4. Pharmacokinetics (PK)

10.4.1. Population pharmacokinetics

As with the other triazoles, the pharmacokinetics of itraconazole are highly variable (see for example (115, 116)). Some of this variability is related to erratic oral bioavailability. Itraconazole exhibits non-linear (or saturable) pharmacokinetics although this is not as well characterised as for voriconazole (117). Itraconazole exhibits prolonged terminal clearance and accumulates slowly. The terminal half-life is approximately 24 hours and the time to steady state may be as long as 14 days (116).

While these estimates are of dubious value for a nonlinear agent, they provide a guide for the time taken to develop serum concentrations that are therapeutic and non-toxic.

A number of population pharmacokinetic models have been developed to describe the PK of itraconazole in various patient populations including bone marrow transplant recipients, cystic fibrosis (118, 119) and HIV positive patients (120). Some models have also estimated the pharmacokinetics of the bio-active metabolite hydroxy-itraconazole. In the majority of cases, linear structural models have been used - this is simply because most datasets do not enable robust estimates for nonlinear pharmacokinetics to be obtained (i.e. a single fixed regimen has been used making it difficult to characterise nonlinear pharmacokinetic behaviour). The most significant consequence of nonlinear pharmacokinetics is the rapid accumulation of drug in those patients with saturated clearance mechanisms.

10.4.2. Absorption

The absorption of itraconazole capsules is facilitated by an acidic environment, which is the basis for recommendations for administration with food or acidic soft drinks (121). The oral bioavailability of itraconazole capsules doubles when administered after food (117, 122). Conversely, absorption is impaired by coadministration with agents that reduce gastric acidity (e.g. proton pump inhibitors) and in achlorhydria (or hypochlorhydria) that is frequently associated with critical illness. There is no food effect with the oral suspension, and oral bioavailability increases in the fasted state (123).

10.4.3. Metabolism

Itraconazole is predominantly metabolised via the cytochrome p450 isoenzyme CYP3A4 with the production of an active metabolite, hydroxyitraconazole.

Other metabolites include keto-itraconazole and N-dealkylitraconazole (124). Hydroxy-itraconazole, the only biologically active metabolite has antifungal potency that is comparable to the parent compound. Concentrations of hydroxy-itraconazole are approximately double those of the parent compound (117).

10.4.4. Disposition

The volume of distribution is approximately 11 L/kg or 700-800 L for an average adult (116). Such a large volume suggests extensive distribution into tissues.

10.4.5. Excretion

Systemically-available itraconazole undergoes extensive oxidative metabolism to form a large number of metabolites, which are subsequently excreted in the bile (116). Approximately 3-18% of itraconazole (non-absorbed) is passed unchanged in the faeces and none is found in the urine (116, 125).

10.4.6. Tissue Pharmacokinetics

The penetration of itraconazole into non-inflamed aqueous compartments (e.g. CSF and aqueous humour) is negligible (126, 127). In the presence of inflammation, drug concentrations may be significantly higher. For example, itraconazole concentrations in the aqueous humour of the inflamed eye increase from virtually zero to ~50% of concomitant serum concentrations (127).

Studies in both laboratory animals and humans consistently report very low concentrations of itraconazole within the CSF (126, 128, 129). Despite this observation, itraconazole clearly has clinically relevant antifungal activity within the CNS. Both itraconazole and hydroxy-itraconazole penetrate the cerebral parenchyma in laboratory animal models of fungal infection (130), but there is a relative paucity of data compared with other agents. Much of the clinical efficacy of itraconazole for CNS infections likely reflects adequate drug concentrations in the cerebrum and meninges rather than the CSF. Itraconazole possesses high affinity to keratin and accumulates in the stratum corneum or the skin (131). Dosages of 100-

200 mg are associated with tissue concentrations in the sebum and stratum corneum that exceed corresponding plasma concentrations by up to ten-fold. Itraconazole concentrations persist in the skin for 3-4 weeks after cessation of antifungal therapy (132). Both itraconazole and hydroxy-itraconazole penetrate various subcompartments of the lung of healthy volunteers, including epithelial lining fluid and pulmonary alveolar macrophages (PAMs) (133). Concentrations in PAMs are 4-5 times higher than those achieved in serum, although the clinical relevance of this finding is not known (133).

10.4.7. Drug-Drug Interactions

Drug-drug interactions with itraconazole occur via several different mechanisms and are an important consideration for the safe and effective use of itraconazole. Agents that inhibit gastric acid secretion, such as antacids, proton pump inhibitors and H2-antagonists all reduce the absorption of itraconazole capsules—these agents should be stopped if at all possible. At the very least, adequate absorption should be verified and an alternative formulation or antifungal agent used if concentrations are low or undetectable. Itraconazole metabolism is accelerated by concomitant administration of rifampicin, phenytoin and carbamazepine, which potentially results in an inability to achieve therapeutic serum concentrations (134). Such a scenario is frequently seen in patients with chronic pulmonary aspergillosis who also have atypical mycobacterial infection that requires a rifampicin-containing regimen. In addition, many clinically significant interactions relate to the suppression of CYP3A4 activity by itraconazole that leads to higher exposures of agents that are metabolised via this route. For example, itraconazole induced inhibition of vincristine metabolism may result in drug accumulation that produces neurological impairment and SIADH (135). Itraconazole also prolongs the action of benzodiazepines, digoxin, cyclosporine, tacrolimus, sirolimus, statins and warfarin (136-139). Significant care must be exercised to avoid untoward effects related to drug interactions.

Interactions between itraconazole and corticosteroids vary from compound to compound. Itraconazole significantly increases methylprednisolone concentrations, but interactions with prednisolone appear minor and do not result in suppression

of the adrenal axis (140, 141). Interactions with inhaled steroids have also been reported, in particular with budesonide and fluticasone and this may be an important consideration for the treatment of allergic fungal disease (142). In a small series of 25 patients receiving itraconazole and inhaled budesonide, approximately 45% of patients developed clinically significant adrenal suppression (143).

10.5. Pharmacodynamics

The pharmacodynamics of itraconazole have been characterised in a well-validated rabbit model of invasive pulmonary aspergillosis (144). Concentrations of itraconazole 6 mg/L (measured two hours post dose by bioassay) are associated with near-maximal reduction in pulmonary fungal burden when estimated using $\log_{10}$ CFU/g lung (144). Similarly, a concentration of 3.72 mg/L is associated with half- maximal reduction in fungal burden. The implication of these results for humans are slightly difficult to interpret because the usual clinical measure of drug exposure in clinical settings is a trough concentration measured using HPLC.

In clinical studies, steady-state trough concentrations of 0.25 mg/l (measured by HPLC) were initially considered sufficient for the prevention of invasive fungal infections in neutropenic patients (145). Subsequently, higher trough concentrations of 0.5 mg/l were proposed on the basis of minimum inhibitory concentrations of itraconazole against *Aspergillus* spp. (146). Trough concentrations > 0.5 mg/L are associated with improved clinical outcomes for patients with mucocutaneous disease (147). Itraconazole concentrations of >5 mg/L (estimated using bioassay) are associated with improved survival of patients with invasive aspergillosis (148).

10.6. Clinical Use and Efficacy

The clinical uses and recommended regimens for itraconazole are summarised in Table 1.

Table 1. Clinical indications and regimens of itraconazole

Diagnosis	**Doses and length of treatment**
Vulvovaginal candidiasis	200 mg twice daily for 1 day
Oropharyngeal candidiasis	200 mg daily for 1 week
Dermatophyte infections	*Tinea corporis*, *tinea cruris* and pityriasis versicolor: 200 mg twice daily for 7 day; *Tinea pedis/manuum*: 100 mg once daily for 30 days or 200 mg twice daily for 7 days; Onychomycosis: 200 mg once daily for 3 months or pulse therapy (200 mg twice daily for 7 days repeated after 21 days).
Prophylaxis in HIV and neutropenia due to haematological malignancy or bone-marrow transplantation	200 mg daily, increased to 400 mg if proven low circulating levels; Oral solution 5 mg/kg daily in 2 divided doses Continued until neutrophil count or CD4 count recovers
Invasive aspergillosis	Intravenous 200 mg every 12 hours for 2 days, then 200 mg once daily for maximum 12 days. Oral 600mg three times daily for 4 days then 200mg twice daily.
Chronic pulmonary aspergillosis	200 mg daily, usually life-long treatment required
Allergic bronchopulmonary aspergillosis	200 mg twice daily for 4-6 months followed by 4-6 months tapered dose, longer course if relapses occur
Blastomycosis	200-400 mg for 8–12 months
Sporotrichosis	100-400 mg for 3-18 months

Histoplasmosis	Oral 200 mg three times daily for 3 days, then 200 mg once or twice daily; Intravenous 200 mg every 12 hours for 2 days, then 200 mg once daily for maximum 12 days
Coccidioidomycosis	200-600 mg daily for 8-12 months
Paracoccidioidomycosis	200 mg orally once a day for 6 months
Systemic mycoses due to *Talaromyces marneffei*	Consolidation therapy in severe disease: 400 mg daily for 10 weeks; Mild to moderate disease: 400 mg/day as monotherapy for 8 weeks then 200 mg daily until CD4 count are >100/uL for over 6 months
Chromoblastomycosis	200-400 mg/day until disappearance of lesions
Cryptococcosis	200-400 mg daily for 6-12 months (only in mild-moderate pulmonary disease); 400-600 mg for maintenance/prophylaxis following induction and consolidation therapy in cryptococcal meningitis.
Systemic candidiasis	100-200 mg daily

10.6.1. Prevention of invasive fungal infections in immunocompromised patients

Oral itraconazole is licensed for the prevention of fungal infection in the presence of HIV or prolonged neutropenia where invasive mould infections are likely (fluconazole, the commonly used alternative oral agent, is not active against *Aspergillus* spp.). The safety and efficacy of itraconazole for the prevention of invasive fungal infections has been extensively studied. Much of the early clinical experience was inconclusive because the trials were not powered to detect any difference in mortality. Nevertheless, a meta-analysis of 3,597 patients from 13 clinical trials demonstrated that oral itraconazole, given as suspension, prevents invasive fungal infections and is also associated with decreased fungal associated mortality (87). Importantly, the protective benefit of itraconazole is likely related to the greater systemic drug exposure that is achieved with the oral suspension - the

protective benefit is only present with the use of itraconazole suspension as opposed to the capsule formulation. More recently, there have been a number of well-designed and appropriately powered clinical trials comparing itraconazole with fluconazole (149, 150). These trials suggest that itraconazole is an effective agent for preventing mould infections, but those adverse events including gastrointestinal intolerance and deranged liver function tests are frequently seen. Children and adults with chronic granulomatous disease are routinely given long-term itraconazole to prevent the most common cause of death, invasive aspergillosis.

10.6.2. Acute invasive aspergillosis

Invasive aspergillosis remains a significant public health problem. The development of itraconazole was a significant advance for the management of invasive aspergillosis because it provided an orally bioavailable alternative to amphotericin B deoxycholate. There are only limited data supporting the use of itraconazole for primary treatment of invasive aspergillosis, and no randomised clinical trials. Itraconazole 600 mg/day for 4 days followed by 400 mg/day appears effective for treatment of invasive aspergillosis (148) although diagnostic criteria and criteria for clinical response have changed over the past 20 years making comparisons with current agents somewhat difficult. Itraconazole (i.v. followed by oral capsules) is effective as salvage therapy for invasive pulmonary aspergillosis in a variety of clinical settings including profoundly immunocompromised patients, chronic granulomatous disease and AIDS (68).

10.6.3. Chronic pulmonary aspergillosis

Chronic pulmonary aspergillosis is a debilitating infection with 75-80% five-year mortality (151). The pathogenesis is distinct from acute invasive disease and involves the infection of pre-existing cavities by *Aspergillus* spp, with subsequent slow destruction of the lung with either cavity expansion or fibrosis. Patients frequently require life-long antifungal therapy. Itraconazole is frequently used as a first-line agent (151). Capsules or oral suspension can be used; the limitations of these formulations include difficulties in achieving therapeutic drug concentrations and poor tolerability, respectively. Resistance to itraconazole has been

documented following long-term therapy, and this usually mandates use of an alternative antifungal agent (108).

10.6.4. Dermatophyte infections

Prolonged or intermittent courses of oral itraconazole are used in the treatment of widespread cutaneous, hair and nail infections. Itraconazole can be used for dermatophyte infections, although it has been largely superseded by newer agents such as terbinafine (152-154). Only griseofulvin is included in the list of WHO essential medicines. Itraconazole is recommended as first line therapy for HIV-associated eosinophilic folliculitis and as second line therapy for tinea (dermatophyte infections) (155). It is equivalent to terbinafine in the treatment of onychomycosis (80).

10.6.5. Endemic Fungi

Itraconazole is a first-line agent for the treatment of many endemic mycoses including blastomycosis, sporotrichosis, histoplasmosis, paracoccidioidomycosis and coccidioidomycosis. Doses of 200-600 mg daily for 8-12 months are used in the majority of cases (see table 1) (72, 78). A loading dose is used in some specific circumstances (e.g. disseminated histoplasmosis) (71). Itraconazole is a first line agent for the treatment of histoplasmosis caused by *Histoplasma capsulatum* and *capsulatum* var. *duboisii*.

Sporothrix spp. isolates are highly susceptible to itraconazole (75). Itraconazole is a first-line agent for the treatment of both localised and disseminated sporotrichosis. Prolonged oral therapy (typically 3-18 months) of itraconazole 100-400 mg daily is effective in 80-95% of patients (76).

Similarly, itraconazole is the treatment of choice for pulmonary and disseminated blastomycosis caused by *Blastomyces dermatitidis*. Treatment regimens of 200-400 mg for 8–12 months are effective in up to 90% of patients. Patients with severe disseminated disease or CNS disease should be initially treated with amphotericin B deoxycholate for 1–2 weeks followed by itraconazole 400 mg for at least 12 months (69).

For Paracoccidioidomycosis, itraconazole has been extensively used, and recently demonstrated in a large retrospective series to provide 35% higher cure rate than cotrimoxazole (156).

Itraconazole is a first-line agent for the treatment of coccidioidomycosis and has equivalent efficacy equal to fluconazole. Itraconazole may be superior for the treatment of skeletal lesions (71). Dosages of 100-400 mg daily have been used for up to many months or years. Long-term therapy is necessary for chronic cavitary pulmonary coccidioidomycosis and coccidioidal meningitis.

10.6.6. Cryptococcal meningitis

Itraconazole has potent in vitro activity against *Cryptococcus neoformans*, and is effective in laboratory animal models of cryptococcal meningitis (126). The efficacy of itraconazole for the prevention of cryptococcal meningitis in patients with AIDS has been studied in Thailand where there are additional concerns regarding *Talaromyces* (*Penicillium) marneffei* (157). In this context, itraconazole appears effective, although it is not widely used for this indication. Itraconazole is not used for induction therapy (polyenes alone or in combination with flucytosine are generally used for this purpose), although there is some evidence that itraconazole 200 mg b.i.d-200 mg t.i.d (depending on serum concentrations) can be used for this indication (158).

Similarly, itraconazole is generally not used for consolidation therapy. A trial comparing fluconazole and itraconazole (both 200mg daily) for consolidation therapy was stopped early because of the higher rate of relapse in the itraconazole arm (23 vs. 4%; p=0.006) (159). In contrast, however, itraconazole 200 mg bid following a loading dose of 600 mg/day for three days has been used successfully for this indication in another clinical trial (160).

Collectively, therefore, itraconazole is not used as first-line agent for either induction or maintenance therapy for cryptococcal meningitis (161). The potential reasons that may account for suboptimal clinical outcomes despite demonstrated in vitro and in vivo activity include sub-therapeutic systemic drug exposure, suboptimal penetration into the CSF, reduced in vitro susceptibility of some isolates and the use of relatively low dosages (e.g. 200 mg/day) (158). In the HIV

setting, there are fewer drug interactions with fluconazole, but in areas endemic for histoplasmosis and penicilliosis, itraconazole would be a preferred choice.

10.6.7. Systemic mycoses due to Talaromyces Marneffei

Disseminated infections caused by *T. marneffei* (Penicilliosis) in HIV-positive patients with AIDS is usually treated with amphotericin B deoxycholate (0.6 mg/kg) for 2 weeks followed by oral itraconazole 400 mg per day for 10 weeks. For mild disease itraconazole 400 mg/day as monotherapy for 8 weeks can be used, followed by maintenance therapy with 200 mg per day to prevent relapse until CD4 count are >100/uL for over 6 months (79). Treatment with itraconazole alone has also been shown to be effective for all forms of infection, but is associated with a marginally higher rate of relapse (77). Itraconazole is erratically absorbed in patients with AIDS patients who have variable gastric pH (162). Furthermore, there is limited information on the pharmacokinetics of generic formations of itraconazole that are widely used in South East Asia.

10.6.8. Allergic Fungal Syndromes (asthma and ABPA)

Itraconazole is increasingly used for the treatment of allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) (163, 164). Two randomised placebo controlled studies demonstrated significant benefits of itraconazole, and a further placebo-controlled study in SAFS also demonstrated benefit (28). Relapse following discontinuation of itraconazole is common. Itraconazole acts partly as a corticosteroid-sparing agent, although some patients have major interactions of inhaled corticosteroids, leading to adrenal insufficiency subsequently.

The role of antifungals in allergic fungal sinusitis is minor, reserved only for recalcitrant and recurrent disease, with data based on collected series of problematic patients.

10.7. Use in Special Populations

10.7.1. Neonates and Children

There are relatively limited data describing the use of itraconazole use in infants and older children. A single intravenous or oral dose of itraconazole solution of 2.5

mg/kg/day in children aged 7 months-17 years is well tolerated, but results in considerable variability in drug exposure and trough concentrations <0.5 mg/L measured using HPLC (165). An oral dosage of 5 mg/kg/day results in lower concentrations in infants compared with children > 2 years of age (166). Oral itraconazole solution given 2.5 mg/kg/twice daily is effective for treatment of oropharyngeal candidiasis in HIV positive children (167), and for prevention of invasive fungal infection in children with neutropenia (168).

10.7.2. Renal Insufficiency

Limited data are available on the use of oral itraconazole in patients with renal impairment. A PK study using a single 200 mg dose of i.v. itraconazole in 19 patients with renal impairment (uraemia: n=7; haemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5) suggested no significant effect of haemodialysis or peritoneal dialysis on the pharmacokinetics of itraconazole (169). In moderate to severe uraemia (mean creatinine clearance of 13 mL/min/1.73 m_2) AUCs were slightly reduced compared with estimates obtained from patients with normal renal function. Renal accumulation of cyclodextrin is seen in laboratory animal studies (12). Therefore, use of the i.v. formulation is not recommended in setting of renal impairment although the clinical implications of cyclodextrin accumulation in humans are considered minor.

10.7.3. Hepatic Insufficiency

Itraconazole is predominantly hepatically metabolized. Patients with impaired hepatic function receiving itraconazole require assiduous monitoring. A PK study using a single oral dose of 100 mg daily in cirrhotic subjects demonstrates a statistically significant reduction in the mean Cmax (47%) and a two-fold increase in the elimination half-life (37 + 17 hours vs. 16 + 5 hours) compared with healthy volunteers (170). Drug exposure quantified in terms of the AUC is comparable.

Consideration should be given to the prolonged elimination half-life of itraconazole in cirrhotic patients in the setting of other medications undergoing hepatic metabolism.

10.8. Adverse Events and Toxicodynamics

Toxicodynamic relationships have recently been described (171). A mean serum concentration of 17.1 mg/L (measured by bioassay) splits a population of patients into two groups each with a high and low probability of toxicity. Thus, a mean concentration of 17.1 mg/L provides a useful upper limit for therapeutic drug monitoring and can be used to minimise the probability of toxicity.

Itraconazole is generally reasonably well tolerated, although this is dependent on the formulation that is used. The adverse events from 9065 patients enrolled in all clinical studies published 1987-2008 are summarised in Table 2.

Table 2. Data published between 1987 to 2008 about frequency of adverse effects with itraconazole.

Adverse effect	**Cumulative data**	**Percentage**
	n = 9065	
Gastrointestinal		
GI upset[1]	1658	18.3
Abnormal Liver function test[2]	416	4.6
Structural liver change	1	0.01
Renal		
Renal impairment[3]	43	0.47
Polyuria/urinary frequency	7	0.07
Metabolic disorders		
Hypokalaemia	202	2.2
Hypertriglyceridaemia/hypercholesterolaemia	18	0.20
Hypomagnesaemia	14	0.14
Hyponatraemia	10	0.11
Hyperkalaemia	8	0.09
Elevated uric acid	7	0.07
Cutaneous		

Rash/pruritus	250	2.76
Alopecia	19	0.20
Site reactions/vasculitis	4	0.04
Steven-Johnson syndrome	2	0.02
Hirsuitism	1	0.01
Photosensitivity	1	0.01
Diaphoresis	1	0.01
Psychiatric/neurological		
Headache	111	1.22
Cognitive/mood/sleep disturbance[4]	24	0.26
Dizziness	22	0.24
Taste disturbance	15	0.16
Seizure	8	0.09
Tinnitus	4	0.04
Visual disturbance[5]	4	0.04
Peripheral neuropathy	2	0.02
Tremor	1	0.01
Leg weakness	1	0.01
Cardiovascular		
Hypotension	87	0.96
Peripheral oedema	39	0.43
Dyspnoea	35	0.38
Hypertension	23	0.25
Arrhythmia/palpitations	21	0.23
Haematological		
Leukocytopenia	71	0.78
Anaemia	52	0.57
Thromobocytopenia	15	0.16
Eosinophilia	2	0.02
Endocrine		
Hyperglycaemia	3	0.03

Thyroid dysfunction	1	0.01
Sexual dysfunction[6]	16	0.17
Menstrual disturbance	15	0.16
Gynaecomastia	5	0.05
Weight gain	3	0.03
Breast tenderness	1	0.01
Pathological fracture	1	0.01
Symptomatic adrenal suppression	1	0.01
Striae/bruising	1	0.01
Systemic/other		
Fever/rigors	75	0.82
Malaise/fatigue/myalgia	19	0.2
Rhabdomyolisis	3	0.03
Pancreatitis	1	0.01

[1]Including abdominal pain, nausea, vomiting, diarrhoea, constipation

[2]Including increased alanine transaminase, aspartate transaminase, alkaline phosphatase, bilirubin, lactate dehydrogenase

[3]Including increased creatinine, blood urine nitrogen, proteinuria

[4]Including euphoria, depression, disturbed concentration, insomnia, hypersomnia

[5]Including photophobia and blurred vision

[6]Including impotence and reduced libido

Gastrointestinal symptoms occur in ~20% of patients, which has a significant impact upon compliance. Cardiac failure is a serious, albeit relatively uncommon adverse event. In some cases reversible depressed left ventricular function has been documented with echocardiography (172). The mechanism is unknown. More commonly, itraconazole causes isolated peripheral oedema that is reversible with cessation of drug. Itraconazole can cause hepatic inflammation, which may manifest as a hepatic or obstructive pattern or on occasions a mixed picture. Rare cases of acute hepatic failure have been described, which usually results from

persistent use of itraconazole despite laboratory or clinical evidence of underlying drug induced hepatic inflammation. There may not necessarily be cross reactivity with other triazoles. A non-pruritic maculopapular rash is seen in 5-20% of cases. A range of neurological symptoms has also been described, including headache, sensorimotor peripheral neuropathy, tremor and sleep disturbance. Peripheral neuropathy is especially noted after 3 months of administration and can persist for several months after discontinuation. A range of metabolic and/or endocrinological disturbances have also been documented, including isolated reversible hypo- and hyperkalaemia, hyponatraemia, hypercholesterolaemia and Cushing's syndrome (see table 1).

10.9. Measurement of Itraconazole, Therapeutic Drug Monitoring and Safe Use

Itraconazole concentrations in serum and tissues can be measured by mass spectrometry, high-performance liquid chromatography (HPLC) or bioassay (173, 174).

A bioassay measures both itraconazole and its bioactive metabolite hydroxyitraconazole, while mass spectroscopy and HPLC measures enable concentrations of these species to be separately quantified. Because of the inability to separate the biological effect attributable to the parent compound versus that from the active metabolite, itraconazole concentrations measured by bioassay are typically 2–10 times higher than those estimated using HPLC. Thus, clinicians interpreting itraconazole serum concentrations must know the laboratory method that has been used.

Pharmacodynamic and toxicodynamic relationships have been defined for itraconazole. Therapeutic drug monitoring (TDM) is widely advocated for optimising drug exposure (175, 176). In addition, TDM allows compliance to be assessed, as well as enabling modification of dosing, formulation and administration with food or acidic beverages. Data from clinical trials suggest a reasonable lower therapeutic target for steady-state trough itraconazole levels is 0.5 mg/L measured by HPLC. Where measured by bioassay, a reasonable lower limit for therapeutic drug monitoring is approximately 5 mg/L. Lower target levels

may be required in highly sensitive pathogens such as *Histoplasma capsulatum*, but these have not been formally defined. An upper therapeutic limit of 17.1 mg/L measured by bioassay is likely to optimally limit toxicity (171, 175). No upper limit has been formally defined for concentrations measured using HPLC.

11.Summary of comparative effectiveness in a variety of clinical settings:

11.1. Identification of clinical evidence

(search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Itraconazole began clinical trials in late 1985 and was approved in Europe and the USA in 1991. The authors of this application have over 70 years of collective experience with itraconazole of clinical trials, patient treatment, literature and grant reviews, laboratory monitoring and susceptibility testing and have drawn extensively on that experience in making this application. As of Nov 30th 2014, there are 7,610 papers listed on MedLine with reference to itraconazole, of which 662 are 'clinical trials'. We have not undertaken a separate meta-analysis, relying on those that are published, and in areas where no randomised trial data exists (most indications) on a combination of clinical guidelines, large prospective and retrospective series, and supportive data.

11.2. Summary of available data

(appraisal of quality, outcome measures, summary of results)

The information provided for the clinical trials performed with itraconazole (table 3) has been collected from the following references (69, 71, 79-82, 87, 149, 150, 155, 156, 161, 175, 177-191)

Table 3. Itraconazole clinical trials

Disease	Quality of clinical efficacy data available
Vulvovaginal candidiasis	Randomised controlled studies (capsule) Open
Oropharyngeal candidiasis	Randomised controlled studies (capsule)

Dermatophyte infections	Randomised controlled studies, primarily in onychomycosis. Multiple open prospective studies.
Prophylaxis in HIV and neutropenia due to haematological malignancy or HSCT	Multiple randomised studies in neutropenic patients, HIV/AIDS patients and HSCT recipients.
Invasive aspergillosis	Prospective open studies of oral and intravenous itraconazole
Chronic pulmonary aspergillosis	One small randomised study, multiple retrospective studies
Allergic bronchopulmonary aspergillosis	Two placebo-controlled randomised studies (and another supportive study in SAFS).
Blastomycosis	Open prospective study
Sporotrichosis	Open prospective study
Histoplasmosis	Two prospective studies, including maintenance/suppressive treatment in HIV/AIDS.
Coccidioidomycosis	One randomized study in coccidioidal meningitis, prospective studies for other manifestations.
Paracoccidioidomycosis	Two controlled randomised studies, and other retrospective case series.
Talaromyces marneffei infection	Two controlled randomised studies, one of maintenance therapy after induction treatment and one primary prophylaxis.
Chromoblastomycosis	Small prospective open studies and case series
Cryptococcosis	One primary prospective therapy study, several controlled randomised studies for continuation/maintenance therapy; some prophylaxis studies.
Systemic candidiasis	Randomised controlled studies (IV)

HSCT = haematopoietic stem cell transplantation

11.3. Summary of available estimates of comparative effectiveness

The outcomes of the many studies are summarised in table 4. The endpoints in prophylaxis studies in neutropenia and HSCT patients are not as precise as for therapy studies, because of the difficulties of making a diagnosis in this setting and biomarkers for infection being suppressed by prophylaxis. Endpoints for chronic pulmonary and allergic bronchopulmonary aspergillosis are challenging for several reasons, but mostly because radiology and abnormal *Aspergillus* serology changes slowly, symptoms can fluctuate and there are no really good biomarkers. Likewise in systemic candidiasis, if death occurs, the cause of death is often difficult to discern and autopsy infrequent and often not definitive (69, 71, 79-82, 87, 149, 150, 155, 156, 161, 175, 177-191)

Table 4. Effectiveness of itraconazole clinical trials

Disease	**Summary of overall effectiveness**
Vulvovaginal candidiasis	Response rates >90%, both for single episode and recurrent disease suppression. Equivalent to fluconazole.
Oropharyngeal candidiasis	Response rates >90% for infection in HIV patients, equivalent to fluconazole and ~70% for fluconazole resistant oropharyngeal candidiasis (oral suspension). In cancer patients, response rates were ~60% for itraconazole and 74% for fluconazole.
Dermatophyte infections	Response rates ~95% and ~70% for fingernail and toenail onychomycosis, equivalent or slightly inferior to terbinafine, but superior to fluconazole. Responses *tinea* infections >95%, similar to terbinafine. Response to pityriasis versicolor and HIV-associated eosinophilic folliculitis >90%, better than topic therapies.
Prophylaxis in HIV and neutropenia due to	Protection against mucosal and invasive candidiasis >90% in all groups. No demonstrated protection in

haematological malignancy or HSCT	neutropenic patients with capsules against invasive aspergillosis, but ~50% protection with oral suspension (better bioavailability). Excellent protection in HIV/AIDS patients against histoplasmosis, cryptococcal meningitis and *T. marneffei infection*.
Invasive aspergillosis	Approximately 40% efficacy for invasive aspergillosis, probably equivalent to amphotericin B, but may be less effective than voriconazole.
Chronic pulmonary aspergillosis	75% stable and improvement rate compared with 30% in a small RCT. Overall about a 60% response rate, depending on response criteria, similar to other agents (amphotericin B, voriconazole and micafungin).
Allergic bronchopulmonary aspergillosis	60% response rates with a high relapse rate after therapy discontinuation, for both ABPA and SAFS.
Blastomycosis	>95% response rate over 6 months.
Sporotrichosis	>95% response rate over 3-6 months, much superior to potassium iodide and fluconazole, but equivalent to terbinafine.
Histoplasmosis	>80% in non-immunocompromised patients compared with 63% with fluconazole. 85% response in HIV/AIDS, especially in milder cases, superior to high dose fluconazole (74%) but not amphotericin B. Suppression/maintenance therapy in AIDS >95% effective, compared with ~70% for fluconazole.
Coccidioidomycosis	In coccidioidal meningitis, 50% responded to fluconazole and 63% to itraconazole over 8 months. In non-pulmonary, non-meningeal coccidioidomycosis, response rates were >90%; in

	chronic pulmonary coccidioidomycosis, response rates were ~50%.
Paracoccidioidomycosis	>90% response rates, with a faster response time than sulphadiazine or cotrimoxazole.
Talaromyces marneffei infection	97% response rate to amphotericin B followed by itraconazole, and superior protection to systemic fungal infections in HIV patients with CD4 counts <100 (98% itraconazole vs 83% placebo).
Chromoblastomycosis	~40% response rates, often supplemented by heat treatment.
Cryptococcosis	~40% response rate, inferior to amphotericin B and flucytosine as primary therapy of cryptococcal meningitis in AIDS. Maintenance therapy is as effective as fluconazole if ≥400mg/d itraconazole is given.
Systemic candidiasis	Equivalent to fluconazole in a small paediatric randomised study, with response rates ~80% and mortality of 9-13%. In adults in intensive care, a prospectively enrolled population showed success in 61.5% patients (66% first-line and 50% second-line therapy). Not recommended for prophylaxis is intensive care patients.

Taking in consideration all studies performed, itraconazole has been approved by international agencies for the treatment of many fungal infections

A. Capsules are approved for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:
    - Blastomycosis, pulmonary and extrapulmonary
    - Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non- meningeal histoplasmosis, and;
    - Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

B. Capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients:
    - Onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (*tinea unguium*), and
    - Onychomycosis of the fingernail due to dermatophytes (*tinea unguium*).

C. Oral solution is approved for the treatment of:
    - Prophylaxis of fungal infections in neutropenic patients and following haematopoietic transplantation;
    - Treatment of oropharyngeal and oesophageal candidiasis, including fluconazole resistant disease;

D. Intravenous solution is approved for the treatment of:
    - Empiric treatment of febrile neutropenic patients with suspected fungal infections
    - Treatment of blastomycosis, histoplasmosis and aspergillosis

In addition, itraconazole has been also recommended in different guidelines for the treatment of:

- According the Aspergillosis guidelines of the Infectious Diseases Society of America, itraconazole is recommended as primary treatment for (190)
    1. Chronic cavitary pulmonary aspergillosis;
    2. Aspergilosis bronchopulmonary allergic (ABPA);
    3. Allergic *Aspergillus* sinusitis.
- And as alternative treatment (in all cases, except for *Aspergillus* infections of the eye, where intraocular amphotericin B deoxycholate is the preferred treatment) in the following conditions (Note: none of antifungals recommended as primary or alternative in these and other guidelines are included in EML list) Invasive aspergillosis;
    1. Invasive sinus aspergillosis;
    2. Tracheobronchial aspergillosis;
    3. Subacute invasive pulmonary aspergillosis;
    4. Aspergillosis of CNS;

5. *Aspergillus* infection of the heart (endocarditis, pericarditis, and myocarditis);
6. *Aspergillus* osteomyelitis and septic arthritis;
7. *Aspergillus* infections of the eye (endophthalmitis and keratitis);
8. Cutaneous aspergillosis;
9. Aspergillus peritonitis;
10. Empirical and preemptive antifungal therapy;
11. Prophylaxis against invasive aspergillosis;
12. Aspergilloma;

- According to the Guideline for the management of *Candida* diseases in HIV-infected patients (181), itraconazole oral solution is recommended for the treatment of refractory oropharyngeal and oesophageal candidiasis with AII grade. Fluconazole is the election treatment for first episodes of oropharyngeal, oesophageal candidosis and suppressive therapy with AI grade. Fluconazole is not recommended for the treatment of refractory oropharyngeal and oesophageal candidiasis. Other antifungals included in the guideline are not available in EML, except amphotericin B deoxycholate but with levels of recommendation of DIII for the treatment of refractory oropharyngeal and oesophageal candidiasis or CIII for suppressive therapy.
- According to the ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: prevention and management of invasive infections in neonates and children caused by *Candida* spp. (182), itraconazole suspension is recommended for the primary prophylaxis of invasive candidiasis with a grade BII in children with allogeneic HSCT and AML and recurrent leukaemia. Fluconazole is recommended with an AI grade but should only be used if the institutional incidence of invasive mould infections is low, or if there are active diagnostic and therapeutic algorithms for moulds. Other antifungals recommended are not available in EML list.
- According to Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America, An Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients and Guidelines for the Prevention

and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Histoplasmosis(79, 178, 191), itraconazole is recommended for the treatment of the following clinical patterns of histoplasmosis:

1. Itraconazole is recommended as consolidation treatment for:
    a. Moderately severe to severe acute pulmonary histoplasmosis (AIII);
    b. Moderately severe to severe progressive disseminated histoplasmosis (AI);
    c. CNS histoplasmosis (BIII);
2. Itraconazole is recommended as primary treatment for:
    a. Mild to moderate acute pulmonary histoplasmosis with symptoms for more than 4 weeks (BIII);
    b. Chronic Cavitary pulmonary Histoplasmosis (AIII);
    c. Moderately severe to severe pericarditis (BIII);
    d. Mediastinal lymphadenitis with symptoms for more than 4 weeks (BIII);
    e. Symptomatic mediastinal granuloma (BIII);
    f. Mild to moderate progressive disseminated histoplasmosis (AII);
3. Primary Prophylaxis in patients with CD4 count <150 cells/mm3 and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) (BI);
4. Long-term suppressive therapy (secondary prophylaxis)
    a. For patients with severe disseminated or CNS infection after completion of at least 12 months of treatment (AIII);
    b. In patients who relapsed despite appropriate initial therapy (BIII);

- According to the Clinical Practice Guidelines for the Management of Blastomycosis: 2008 Update by the Infectious Diseases Society of America and An Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients (69, 191), itraconazole

is recommended for the treatment of the following clinical manifestations of blastomycosis

1. Itraconazole is recommended as consolidation treatment for:
    a. Moderately severe to severe pulmonary blastomycosis (AIII);
    b. Moderately severe to severe disseminated blastomycosis (AIII);
    c. CNS blastomycosis (BIII);
    d. Immunosuppressed patients (AIII);
    e. Children with moderately severe to severe blastomycosis (BIII);
2. Itraconazole is recommended as primary treatment for:
    a. Mild to moderate disseminated blastomycosis (AII);
    b. Mild to moderate pulmonary blastomycosis (AII);
    c. Children with mild to moderate disease (BIII);
    d. Skin disease;
    e. Bone disease;

- According to the Practice Guidelines for the Treatment of Coccidioidomycosis and An Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients (183, 191), itraconazole is recommended for the treatment of the following clinical presentations of coccidioidomycosis:
    1. Itraconazole is recommended as consolidation treatment for:
        a. Diffuse pulmonary infection;
    2. Itraconazole is recommended as primary treatment for (fluconazole is also recommended as primary therapy for all these clinical pictures):
        a. Primary pulmonary;
        b. Pulmonary nodule in immunosuppressed patients;
        c. Pulmonary cavity;
        d. Disseminated infection;
        e. Meningitis;

- According to Clinical Practice Guidelines for the Management of Sporotrichosis: 2007 Update by the Infectious Diseases Society of America and An Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients (179, 191), itraconazole is recommended for the treatment of the following clinical manifestations of sporotrichosis:
    1. Itraconazole is recommended as consolidation treatment for:
        a. Pulmonary (AIII);
        b. Meningitis (BIII);
    2. Itraconazole is recommended as primary treatment for:
        a. Lymphocutaneous/cutaneous (AII);
        b. Osteoarticular (AII);
        c. Children with mild disease (BIII);
- According to an Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients (191), itraconazole is recommended for the treatment of disseminated and mild to moderate or slowly progressive Paracoccidioidomycosis (BII);
- According to Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Geographic Opportunistic Infections of Specific Consideration. Penicilliosis marneffei (79), itraconazole is recommended for the treatment of the following clinical presentations of infections caused by *Talaromyces marneffei*
    1. Primary prophylaxis in patients with CD4 count <100 cells/mm3 who reside or stay for a long period in northern Thailand, Vietnam, and Southern China, in particular in rural areas (BI);
    2. Mild disease;
    3. Chronic maintenance therapy (secondary prophylaxis);
- According to WHO Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults (155), itraconazole is recommended for:
    1. The treatment of eosinophilic folliculitis;
    2. When extensive *tinea* infection of hair or nail is non responsive to itraconazole;

- According the British Association of Dermatologists' guidelines for the management of *tinea capitis* 2014 (80), itraconazole is recommended as a second line therapy for the treatment of *tinea capitis* after terbinafine or griseofulvin.

12.Summary of comparative evidence on safety

12.1. Estimate of total patient exposure to date

Itraconazole was licensed in 1991 in Europe and USA. Itraconazole has been used extensively for the prophylaxis and treatment of fungal infections including vaginal thrush, oropharyngeal and oesophageal candidiasis, fungal skin infections, invasive aspergillosis, chronic pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, sporotrichosis, penicilliosis, cryptococcosis, blastomycosis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis and systemic candidiasis. Probably 100's of millions of patients have received treatment.

12.2. Description of the adverse effects

(reactions and estimates of their frequency)

The adverse event profile of itraconazole differs slightly from fluconazole, the only triazole on the EML. High blood levels/exposure of itraconazole are associated with higher rates of many well described side-effects but the treatment doses used for mucosal candidiasis, sporotrichosis, histoplasmosis in non-AIDS patients, blastomycosis, paracoccidioidomycosis (i.e. $\leq$200mg daily) have a low side effect profile. Doses of $\geq$400mg daily (orally) are more commonly associated with adverse events.

12.2.1. Immediate adverse events

There are more gastro-intestinal side effects with itraconazole than with fluconazole, which is especially marked in neutropenic and HST patients receiving itraconazole suspension for prophylaxis. The rate of hepatic dysfunction is almost the same and <5%, depending on the patient group. Prolonged QT interval is described, and is exacerbated by electrolyte disturbance, those with cardiac problems and with other medications that have the same effect. A non-pruritic

rash or an acneiform facial eruption may rarely occur. Itraconazole is much better tolerated than potassium iodide, which is used for sporotrichosis.

12.2.2. Short term adverse events

Ankle oedema is relatively common in older people taking itraconazole for several weeks. Occasionally congestive cardiac failure occurs. Mild hypertension is seen in some patients. Hypokalaemia with weakness may occur, as may general fatigue. Hypokalaemia and renal impairment are much more frequent with amphotericin B. Sleep disturbance is uncommon.

12.2.3. Long term adverse events

Once patients have been taking itraconazole for >3 months, liver function abnormalities are very uncommon. Peripheral neuropathy may be more common than fluconazole, and is probably more common than voriconazole and posaconazole. Hair loss is an occasional severe problem. Erectile dysfunction also can be problematic.

Table 5. Data published between 1987 to 2008 about frequency of adverse effects with itraconazole

Adverse effect	Cumulative data	Percentage
	n = 9065	
Gastrointestinal		
GI upset[1]	1658	18.3
Abnormal Liver function test[2]	416	4.6
Structural liver change	1	0.01
Renal		
Renal impairment[3]	43	0.47
Polyuria/urinary frequency	7	0.07
Metabolic disorders		
Hypokalaemia	202	2.2
Hypertriglyceridaemia/hypercholesterolaemi	18	0.20

a		
Hypomagnesaemia	14	0.14
Hyponatraemia	10	0.11
Hyperkalaemia	8	0.09
Elevated uric acid	7	0.07
Cutaneous		
Rash/pruritus	250	2.76
Alopecia	19	0.20
Site reactions/vasculitis	4	0.04
Steven-Johnson syndrome	2	0.02
Hirsuitism	1	0.01
Photosensitivity	1	0.01
Diaphoresis	1	0.01
Psychiatric/neurological		
Headache	111	1.22
Cognitive/mood/sleep disturbance[4]	24	0.26
Dizziness	22	0.24
Taste disturbance	15	0.16
Seizure	8	0.09
Tinnitus	4	0.04
Visual disturbance[5]	4	0.04
Peripheral neuropathy	2	0.02
Tremor	1	0.01
Leg weakness	1	0.01
Cardiovascular		
Hypotension	87	0.96
Peripheral oedema	39	0.43
Dyspnoea	35	0.38
Hypertension	23	0.25
Arrhythmia/palpitations	21	0.23
Haematological		

Leukocytopenia	71	0.78
Anaemia	52	0.57
Thromobocytopenia	15	0.16
Eosinophilia	2	0.02
Endocrine		
Hyperglycaemia	3	0.03
Thyroid dysfunction	1	0.01
Sexual dysfunction[6]	16	0.17
Menstrual disturbance	15	0.16
Gynaecomastia	5	0.05
Weight gain	3	0.03
Breast tenderness	1	0.01
Pathological fracture	1	0.01
Symptomatic adrenal suppression	1	0.01
Striae/bruising	1	0.01
Systemic/other		
Fever/rigors	75	0.82
Malaise/fatigue/myalgia	19	0.2
Rhabdomyolisis	3	0.03
Pancreatitis	1	0.01

- [1]Including abdominal pain, nausea, vomiting, diarrhoea, constipation
- [2]Including increased alanine transaminase, aspartate transaminase, alkaline
- phosphatase, bilirubin, lactate dehydrogenase
- [3]Including increased creatinine, blood urine nitrogen, proteinuria
- [4]Including euphoria, depression, disturbed concentration, insomnia,
- hypersomnia
- [5]Including photophobia and blurred vision
- [6]Including impotence and reduced libido

12.3. Identification of variation in safety that may relate to health systems and patient factors

There are no known ethnicity or gender specific toxicities. Some toxicities are more common in older people, especially QT prolongation, congestive cardiac failure, ankle oedema and hypertension. Itraconazole has a large number of potential drug:drug interactions, the most important of which related to a loss of activity of given with a rifamycin and certain anticonvulsants. Increased exposure to other drugs is common and some of these are problematic, notably warfarin, digoxin, oral hypoglycaemics and inhaled corticosteroids.

In HIV infected patients there are important interactions with antiretrovirals. There are potential moderate interactions with the following antiretrovirals: Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Ritonavir, Tipranavir, Delavirdine, Efavirenz, Etravirine, Nevirapine, Maraviroc. NNRTIs are the problem. Coadministration of itraconazole (200 mg twice daily) and efavirenz (600 mg once daily) decreased itraconazole Cmax (37%), AUC (39%) and Cmin (44%). Cmax, AUC and Cmin of the metabolite hydroxyitraconazole decreased by 35%, 37%, and 43%, respectively. There was no change in efavirenz Cmax, AUC or Cmin. Case reports +/- Therapeutic drug monitoring do not help on a programmatic level, as there are no data on whether dose increment will overcome the induction. Boosted protease inhibitors (PIs) are easier to handle; a maximum itraconazole daily dose of 200mg is recommended as atazanavir increases itraconazole exposure (192).

12.4. Summary of comparative safety against comparators

Amphotericin B has more side effects than itraconazole, notably immediate infusion related tolerance and renal dysfunction and failure. Itraconazole is used as consolidation therapy after amphotericin B for some fungal diseases.

Fluconazole has fewer side effects than itraconazole but it is only useful for treating fungal infections caused by yeasts. Fluconazole has no activity against filamentous fungi such as *Aspergillus* spp. There is no azole drug with activity against filamentous fungi included in the essential medicines list.

Itraconazole has a different side effect profile from griseofulvin. The most common side effects of griseofulvin are nausea, vomiting, diarrhoea, heartburn, flatulence,

cracking at the side of the mouth, soreness and/or blackening of the tongue and thirst. Headache is a frequent side effect (<15%), but may resolve on continued therapy. Other neurological side effects such as peripheral neuropathy may occur. Maculopapular, urticarial or photosensitivity rashes occasionally occur. Griseofulvin is contraindicated in systemic lupus erythematosus because of excess cutaneous lesions. Hepatotoxicity is infrequent but pre-existing liver disease may be exacerbated by griseofulvin.

13. Summary of available data on comparative costs and cost-effectiveness within the pharmacological class or therapeutic group

13.1. Range of costs of the proposed medicine

We sought information for all countries with a population >1 million (n= 163). We extracted itraconazole availability from Martindale: The Complete Drug Reference, MedIndia.com, MIMS (www.mims.com) and the WHO website (www.who.int). The majority of information, especially local purchase price, was contributed via individual country contacts. All these data were tabulated and prices converted to US$ using conversion rates on XE.com. Data were displayed using StatPlanet (StatSilk, Australia) on the Global Action Fund for Fungal Infections (GAFFI) website at www.gaffi.org/why/burden-of-disease-maps/. The daily price of itraconazole (400mg orally) varied from less than $0.01 in Zambia to $105.50 in Sweden, with a median cost of $6.73. While currency fluctuations may account for some of this variation, the main factor in local cost of itraconazole is the pharmaceutically set retail price.

13.2. Resource use and comparative cost-effectiveness presented as range of cost per routine outcome

The following cost-effectiveness studies have been done with itraconazole, in most cases prior to generic formulations being launched. Only one study has been done in a developing country.

Cost-effectiveness analysis of terbinafine, itraconazole and fluconazole for onychomycosis (Canada – international):

"Each of the new antifungal agents is more cost-effective than griseofulvin for the treatment of onychomycosis and is associated with high compliance, in part because of the shorter duration of therapy." (18)

and

"Efficacy was determined by meta-analysis of the published literature for those studies where appropriate treatment regimens for onychomycosis were put to use. Efficacy outcome measures were limited to mycologic cure rates in the more recalcitrant cases of toenail onychomycosis. From these measures of cost and efficacy, a cost/efficacy ratio was calculated for each drug by dividing the cost per treatment by the weighted average mycological cure rate. This ratio represents the cost per mycologically cured infection. The final outcome measure (the cost per mycologically cured infection) was $2,721, $1,845, and $649, for griseofulvin, itraconazole, and terbinafine continuous therapies, respectively. For itraconazole and terbinafine pulse therapy, the costs were $856 and $389, respectively. For both continuous and pulse therapy, terbinafine is apparently the most cost-effective drug, followed by itraconazole and then by griseofulvin." (193)

13.2.1. For onychomycosis, comparing the topical lacquer with terbinafine and itraconazole (Canada):

"Using the pharmacoeconomic model with three 1-year treatment phases, in which failures or relapses were re-treated with the primary drug, the expected cost per patient was $602 with ciclopirox nail lacquer, $747 with oral terbinafine, and $938 with itraconazole." (194)

13.2.2. Treatment of presumed invasive fungal infections in neutropenic patients (Korea).

"We developed a medical decision analytical tree that included probabilities of toxicity, response and pathogen documentation, and second-line treatments. Clinical data were obtained from randomized clinical trials, and resource use data were obtained from a panel of clinical experts. The total cost of treating presumed invasive fungal infections per neutropenic cancer patient was lower for IV

itraconazole than for conventional amphotericin B, and this lower cost resulted from a reduced need for second-line antifungals. In a cost-effectiveness analysis, IV itraconazole treatment was superior to conventional amphotericin B treatment." (195)

13.2.3. Prevention of invasive fungal infections in neutropenia (Netherlands):

"According to our probabilistic decision model, the monetary benefits of averted healthcare exceed the costs of itraconazole prophylaxis under baseline assumptions (95% CI: from cost-saving to euro 5000 per invasive fungal infection averted). Compared with fluconazole, itraconazole is estimated to be both more effective and more economically favourable, with a probability of almost 98%."(196)

13.2.4. Primary prophylaxis of HIV patients with <150 CD4 counts in a region with a high endemicity for histoplasmosis (French Guiana):

"For a scenario where 12% of patients died, 60% were aware of their human immunodeficiency virus (HIV) infection and adherence was only 50%, primary prophylaxis would prevent 1 death and 9 cases of histoplasmosis for a cost of 36,792 Euros per averted death, 1,533 per life-year saved, 4,415 Euros per averted case, when only counting the costs of itraconazole prophylaxis. Taking into account the total costs of hospitalization showed that primary prophylaxis would allow a savings of 185,178 Euros per year." (197)

14.Summary of regulatory status of the medicine (in various countries)

Itraconazole is available and approved in most countries, but not all, notably Senegal, Algeria, Afghanistan, Barbados, and Eritrea, Gambia, Madagascar, Mongolia. It is approved in Dominican Republic, Iraq, Nepal and Ukraine, but not available. We are unsure about its status in Angola, Armenia, Azerbaijan, Belize, Benin, Bolivia, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Congo, Cook Islands, Costa Rica, Cote d'Ivoire, Cuba, Cyprus, Democratic People's Republic of Korea, Democratic Republic of Congo, Dominica, Equatorial Guinea, Gabon, Ghana, Greenland, Guam, Guinea, Guinea-Bissau, Haiti, Iceland, Republic of Moldova, Morocco, Mozambique, Papua

new Guinea, Paraguay, Puerto Rica, Sierra Leone, Sudan, Syria, Timor-Leste, Turkmenistan, Tanzania, US Virgin Islands, Uzbekistan, West Bank and Gaza Strip, Yemen and Zimbabwe. We will be updating these data over coming months.

15. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopeia)

- British Pharmacopeia. Itraconazole. British National Formulary Sept 2014-March 2015. BMJ Group and Pharmaceutical Press, UK 2014: pp 405-406
- http://www.drugs.com/pro/itraconazole.html
- https://online.epocrates.com

16. Proposed (new/adapted) text for the WHO Model Formulary

Capsules	100 mg
Oral suspension	10 mg/mL
Intravenous formulation	10 mg/ml

We consider that itraconazole has the following indications

1. Prophylaxis, empirical and pre-emptive therapy
    a. Prophylaxis, empirical and pre-emptive therapy against invasive aspergillosis;
    b. Prophylaxis of invasive candidiasis in children with allogeneic HSCT, AML and recurrent leukaemia;
    c. Primary prophylaxis of histoplasmosis in AIDS patients with CD4 count <150 cells/mm3 and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years);
    d. Secondary prophylaxis in AIDS patients with severe disseminated histoplasmosis or CNS infection after completion of at least 12 months of treatment or relapse patients despite appropriate treatment;

e. Primary prophylaxis of infections due to *Talaromyces marneffei* in patients with CD4 count <100 cells/mm3 who reside or stay for a long period in northern Thailand, Vietnam, and Southern China, in particular in rural areas;

f. Secondary prophylaxis of Infections due to *Talaromyces marneffei.*

2. Treatment

a. Chronic cavitary pulmonary aspergillosis;

b. Allergic bronchopulmonary aspergillosis (ABPA);

c. Recurrent Allergic *Aspergillus* sinusitis;

d. Invasive aspergillosis;

e. Invasive sinus aspergillosis;

f. Tracheobronchial aspergillosis;

g. Subacute invasive pulmonary aspergillosis;

h. Cerebral and meningeal aspergillosis;

i. *Aspergillus* infection of the heart (endocarditis, pericarditis, and myocarditis);

j. *Aspergillus* osteomyelitis and septic arthritis;

k. *Aspergillus* infections of the eye (endophthalmitis and keratitis);

l. Cutaneous aspergillosis;

m. Aspergillus peritonitis;

n. Aspergilloma;

o. Refractory oropharyngeal and oesophageal candidosis;

p. Histoplasmosis;

q. Blastomycosis;

r. Coccidioidomycosis;

s. Sporotrichosis;

t. Paracoccidioidomycosis;

u. Infections caused by *Talaromyces marneffei;*

v. Eosinophilic folliculitis in AIDS patients;;

w. Superficial mycoses caused by *Candida*, dermatophytes and *Malassezia*;

x. Onychomycosis.

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