APPLICATION TO ADD ITRACONAZOLE AND VORICONAZOLE 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, there is no any oral drug in the WHO list of essential medicines (WHO EML) which has activity against any filamentous fungi including *Aspergillus* spp. Itraconazole, an azole oral antifungal is the agent of choice for chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis and chromoblastomycosis. Multiple generic capsule forms of itraconazole are available (oral solution and intravenous drug are still branded products). The 19th edition of WHO model of essential medicines list currently includes an azole as antifungal medicine, fluconazole. Although fluconazole is listed under the square box symbol, fluconazole does not have similar clinical performance within azole class of antifungals because is only fully effective for infections caused by some yeast species, notably *C. albicans, C. parapsilosis and C. tropicalis*. High rates of secondary resistance to fluconazole in *C. glabrata* and intrinsic resistance in *C. krusei* are well-known. It is inactive against most of the infections caused by filamentous fungi.

- Fluconazole is ineffective against the following diseases:
    a. Chronic pulmonary aspergillosis;
    b. Acute invasive aspergillosis;
    c. Histoplasmosis;
    d. Sporotrichosis;
    e. Paracoccidioidomycosis;
    f. Systemic mycoses caused by *Talaromyces marneffei;*
    g. Chromoblastomycosis.

Itraconazole has activity against filamentous fungi including species of *Aspergillus*, as well as against fungi causing endemic mycoses and chromoblastomycosis.

Voriconazole is the leading agent for the treatment of invasive aspergillosis and has utility for chronic pulmonary aspergillosis.

This application recommends inclusion of oral itraconazole capsules 100 mg and oral solution 10mg/ml, onto EML and EML for children and voriconazole IV vials 200 mg, oral tablets 50-200 mg and solution 40mg/mL onto the EML and EML for children.

Fluconazole should remain on the EML for the treatment of mucosal candidiasis, including oesophageal candidiasis, cryptococcal meningitis (induction therapy in the absence of amphotericin B and maintenance therapy), candidaemia and urinary candidiasis. It also has utility as a prophylactic agent (for mucosal and deep candidiasis) in leukaemia induction therapy, and is recommended as an alternative to itraconazole solution, typically for itraconazole intolerance. It is also useful for coccidioidomycosis and for some cutaneous fungal infections.

2.1. Summary of findings

2.1.1. Summary of the clinical studies with itraconazole

Disease	**No studies**	**No patients**	**Overall response Mean (range)**	**Comments**
Chronic Pulmonary Aspergillosis	3	57	80% (43.5-82%)	Table 3
Invasive aspergillosis	2	201	57% (39-63%)	Voriconazole is the recommended treatment Table 4
Histoplasmosis	2	96	83.3% (81-85%)	Table 5
Sporotrichosis	3	62	92% (83-100%)	Table 6
Paracoccidioidomycosis	1	81	86.4%	Table 7
T. marneffei	1	74	97.3%	Amphotericin B followed by itraconazole Table 8
Chromoblastomycosis	2	29	72% (63-90%)	Table 9

2.1.2. Summary of the prophylaxis studies with itraconazole

Disease	No studies	No patients	Results
Histoplasmosis	1	295 (149 itraconazole vs 146 placebo)	29 (19%) fungal opportunistic infections in itraconazole group vs 42 (29%) in placebo (p= 0.004; log rank test) Table 5
Systemic mycoses caused by *Talaromyces marneffei*	1	129 (63 itraconazole vs 66 placebo)	1 (1.6%) fungal opportunistic infection in itraconazole group vs 11 (16.7%) in the placebo (p=0.003; log rank test) Table 8

2.1.3. Summary of the clinical studies with voriconazole

Disease	No studies	No patients	Overall response	Comments
Chronic pulmonary aspergillosis	1	41	32%	Table 10
Invasive aspergillosis	1	277	53%	Superior to amphotericin B, with 13% absolute reduction in mortality Table 10

3. Name of the WHO technical department and focal point supporting the application

(where relevant)

- Not applicable

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

- Global Action Fund for Fungal Infection, Rue de l'Ancien-Port 14 1211 Geneva 1, Switzerland, in association with the International League of Dermatological Societies, London, UK, The Manchester University and the Medical Mycology Reference Laboratory of the Instituto de Salud Carlos III.
- David W. Denning (ddenning@gaffi.org)
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- Elizabeth Peers (empeers@gaffi.org)

5. International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

- Itraconazole - ATC Code: J02AC02
- Voriconazole – ATC Code: J02AC03

6. Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate)

6.1. Itraconazole

- Capsules 100 mg for oral administration;
- Oral Solution 10 mg/ml.

Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given. Oral solution is more indicated in children and people who cannot swallow. Oral solution also increases availability in AIDS patients and those on PPIs and H2 blockers.

6.2. Voriconazole

- Tablets 50 mg and 200 mg;
- Intravenous solution 200 mg;

- Oral suspension 40 mg/ml.

7. Whether listing is requested as an individual medicine or as a representative of a pharmacological class

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

8. Treatment details (requirements for diagnosis, treatment and monitoring)

8.1. Diagnosis

- Specimens for fungal cultures and other relevant studies (wet mount, histopathology, serology, antigen detection, PCR, imaging) should be obtained before treatment to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other studies are known; however, once these results become available, antifungal therapy should be adjusted accordingly.

8.2. Indications

8.2.1. Itraconazole

Prophylaxis

- Primary prophylaxis of histoplasmosis in AIDS patients with CD4 count <150 cells/mm^3 and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years);
- 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;
- 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;
- Secondary prophylaxis of Infections due to *Talaromyces marneffei.*

Treatment

- Chronic cavitary pulmonary aspergillosis;
- Invasive aspergillosis;
- Histoplasmosis;
- Sporotrichosis;
- Paracoccidioidomycosis;
- Infections caused by *Talaromyces marneffei*;
- Chromoblastomycosis.

8.2.2. Voriconazole

- Chronic pulmonary aspergillosis;
- Invasive aspergillosis.

8.3. Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is widely advocated for optimising drug exposure (1, 2). 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 (1, 3).

Voriconazole has substantial person to person variability in exposure related to different cytochrome P450 genotypes, underlying liver disease, severity of illness, age and drug interactions. Slow metabolisers, certain CYP 2C19 genotypes which are more common in NE Asia, need reduced doses as do many people over 70 years old and those with hepatic disease. In contrast children, especially very young children, need higher doses. High exposure lead to neurotoxicity (confusion) and a higher incidence of hepatic dysfunction. Therefore, TDM is desirable in the majority of patients, especially

the extremes of age and in handling complex drug interactions (1, 2). The ideal trough concentration is from 1.0 to 4-6 mg/L (1)

In a prospective, randomized blinded single-centre trial of TDM during voriconazole therapy in 100 patients, the proportion of voriconazole discontinuation due to adverse events was significantly lower in the TDM group than in the non-TDM group (4% vs 17%; P = 0.02). More importantly, higher rates of complete or partial response were observed in patients managed with TDM (81% vs those without TDM 57%; P = 0.04) (4). Therefore, antifungal TDM may reduce drug discontinuation due to adverse events and improve the likelihood of a therapeutic response. There are no widely validated algorithms on how to dose voriconazole.

Weight-based dosing is recommended to rapidly achieve therapeutic range, with incremental increases and monitoring (i.e., 50% increase in daily dose) for the patient who has trough levels <1 µg/mL. Voriconazole concentrations often increase disproportionately to administered doses due to saturable metabolism in adults. For patients with very low voriconazole levels, coadministering omeprazole (a CYP2C19 inhibitor) has been reported to "boost" voriconazole area under the curve by 41%. Fundamental pharmacokinetics of voriconazole are different in children (linear) than in adults (nonlinear). In paediatric patients weighing <50 kg, higher voriconazole doses are needed] and drug monitoring is paramount (5).

9. Information supporting the public health relevance

9.1. Epidemiological information on disease burden

9.1.1. Chronic pulmonary aspergillosis (caused by *Aspergillus* spp)

Chronic pulmonary aspergillosis is a worldwide problem, estimated to affect over three million people worldwide, of whom ~1.2 million have had tuberculosis (6). Following pulmonary tuberculosis, 25-33% are left with residual cavitation in the lung and of these 10-35% develop chronic pulmonary aspergillosis. Unpublished data indicate an even higher frequency of the key marker of chronic pulmonary aspergillosis (*Aspergillus* antibody) in smear negative tuberculosis, including in HIV positive patients. Underlying problems and risk factors 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) (6). Most patients are not considered immunocompromised (7, 8).

9.1.2. Acute invasive aspergillosis (caused by *Aspergillus* spp)

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 (9). The disease is common in people with acute leukaemia, stem cell (HSCT) 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), lung cancer and autoimmune disorders (such as systemic lupus erythematosus) (10). Other significant risk factors include medical intensive care (immunoparalysis following bacterial infection) (1.1-5.8%), liver failure and severe burns (11). 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.

9.1.3. Histoplasmosis

Histoplasmosis is caused by *Histoplasma capsulatum,* which is a very slow growing fungus.

Disseminated histoplasmosis

In parts of Latin America, disseminated histoplasmosis is the most common opportunistic infection of newly presenting AIDS patients, and occurs throughout the world at a lower frequency (12-14). Some patients present in shock, requiring intensive care, although most have less severe manifestations. Other risk groups include those at extremes of age, and immunosuppression (15). Untreated this is a fatal form infection.

Chronic cavitary Histoplasmosis

Chronic cavitary pulmonary histoplasmosis is an unusual or rare complication of histoplasmosis. At risk patients include those with chronic pulmonary disease, especially COPD (14).

9.1.4. Sporotrichosis

Sporotrichosis caused by *Sporothrix schenckii,* has been reported worldwide with most reported cases from Central and South America and part of China (16, 17). Hyperendemic rural areas may have attack rates of 1 case per 1000 population; at present there is such an epidemic in Rio de Janeiro State, Brazil. 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, with those at risk including farmers, gardeners and forestry workers (17). There is an ongoing zoonotic outbreak affecting thousands of people from feral cats in Brazil caused by *S. brasiliensis*. 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 some patients do not recall any trauma. AIDS may lead to disseminated sporotrichosis (18).

9.1.5. Paracoccidioidomycosis

Paracoccidioidomycosis caused by *Paracoccidioides brasiliensis*, is endemic to Latin America, especially Brazil where there are probably ~ 3,500 cases annually, so <10,000 worldwide (19). Males are affected 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, and smoking probably increases the risk. Many patients with pulmonary paracoccidioidomycosis also have tuberculosis (15, 16). There is a risk of persistent fibrosis of the lung and oral tissues following infection.

9.1.6. Systemic Mycoses due to *Talaromyces marneffei* infection

Systemic mycoses caused by *Talaromyces marneffei* (former known as penicilliosis), a genus shift very recently made from *Penicillium marneffei,* originate from Southeast

Asia (20-23). About 10% of AIDS patients in Hong Kong and ~30% of patients in N. Thailand present with *T. marneffei* infections (24). Patient with AIDS and *T. marneffei* infections present all over the world, following travel. It also occurs in other immunocompromised patients (25). Untreated, it is a potentially fatal condition.

9.1.7. Chromoblastomycosis (Chromo)

Chromo is a cutaneous and subcutaneous mycosis characterized by the appearance of proliferating chronic skin lesions following traumatic implantation of the fungus. Lesions start as nodule or papule that slowly enlarge becoming verrucose and wart-like. Old lesions can be tumorous or cauliflower-like in appearance, and are very disfiguring. Lymphatic and haematogenous dissemination have been described but 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 are 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 (15). Most of the reported cases occur in Latin America, the Caribbean, Asia, Africa and Australia (26-33).

9.2. Assessment of current use

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

Table 1. Clinical indications and regimens of oral itraconazole capsules for adults

Diagnosis	Doses and length of treatment
Chronic pulmonary aspergillosis	200 mg twice daily, for at least 6 months
Invasive aspergillosis	600mg/8h for 4 days then 200mg/12h day
Histoplasmosis	200 mg/8h for 3 days, then 200 mg once or twice daily
Sporotrichosis	100-400 mg/day for 3-18 months

Paracoccidioidomycosis	200 mg 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/μL for over 6 months
Chromoblastomycosis	200-400 mg/day until disappearance of lesions

Itraconazole dosage in children is 5.0–10.0 mg/kg daily in 2 divided doses, not exceeding 400 mg daily for all the indications listed above.

The clinical uses and recommended regimens for voriconazole are summarised in Table 2.

Table 2. Clinical indications and regimens of voriconazole for adults

Diagnosis	**Doses and length of treatment**
Chronic pulmonary aspergillosis	200mg twice daily po, for 6 months or longer
Invasive aspergillosis	Intravenous loaded dose of 6 mg/kg/dose twice daily, followed by 4 mg/kg/dose twice daily for a minimum of 6–12 weeks, largely dependent on the degree and duration of immunosuppression, site of disease, and evidence of disease improvement. Switch to oral therapy 200-300 mg twice daily, usually after 3-30 days of intravenous therapy

Intravenous voriconazole in children should be given at 9 mg/kg loading dose twice daily. Maintenance intravenous dosing in children is 8 mg/kg/day. Oral dosing must be of 9 mg/kg/ day.

9.2.1. Use in Special Populations

Disadvantaged populations

In most part of the world, HIV infection and its accompanying fungal infections, occur in many vulnerable groups including intravenous drug abusers, sex workers, prisoners and those living in urban poverty. Cutaneous and subcutaneous fungal infections, whether linked to HIV or not, are much more common in poor communities, both rural and urban, and in particular chromoblastomycosis and sporotrichosis are more frequent in subsistence farmers.

Children

Itraconazole has frequently been used in cases of superficial and systemic fungal infection in children with few serious side effects being noted despite a wide range of underlying physiologic states. Itraconazole seems to be effective and safe for the treatment of fungal infections in children. The spectrum of adverse events detected is comparable with adults and relatively infrequent (34, 35). Pharmacokinetics of itraconazole oral solution are not significantly different from adults. A lower Cmax and AUC at 24h was detected but those differences were resolved by 14 day of administration (36).

Voriconazole has been safely and effectively used in children down to 2 years of age. Occasional (rare) cases of invasive aspergillosis have been treated in a younger age group, but there are few data. Paediatric pharmacokinetic studies with adult doses have described a linear non-saturable dose-exposure profile for children < 5 years of age. However, at the higher recommended doses, pharmacokinetics in children are non-linear. For this reason, paediatric patients require more than twice the adult dose to achieve comparable blood concentrations. Several paediatric studies have reported an association between improved patient outcomes and a voriconazole trough concentration >1 mg/L (36).

Renal Insufficiency

No itraconazole dose reduction necessary for patients with renal impairment. Voriconazole given intravenously in those with renal impairment allows accumulation of the cyclodextrin carrier molecule. This molecule in high dosage can alter

uroepithelial cells in experimental animals. In clinical practice, this has not ever been problematic and the current advice to allow voriconazole use in those with greatly reduced creatinine clearance is appropriate, especially as the alternative (amphotericin B) is frankly nephrotoxic.

Hepatic Insufficiency

Itraconazole and voriconazole are predominantly hepatically metabolized. Patients with impaired hepatic function receiving itraconazole require assiduous monitoring. For voriconazole, it is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B). Both drugs should only be used in severe hepatic dysfunction if TDM is available with a short turnaround time.

9.3. Target populations

- Chronic cavitary pulmonary aspergillosis;
- Invasive aspergillosis;
- Histoplasmosis;
- Sporotrichosis;
- Paracoccidioidomycosis;
- Infections caused by *Talaromyces marneffei*;
- Chromoblastomycosis.

9.4. Likely impact of treatment of the disease

9.4.1. Chronic pulmonary aspergillosis (caused by *Aspergillus* spp)

- The 5-year survival is about 20% without antifungal treatment (7, 8). 61% of response with itraconazole treatment and 32% of success at 6 months with voriconazole (53% for chronic necrotizing aspergillosis and 14% for chronic cavitary aspergillosis). The respective clinical success rates of voriconazole at end of therapy were 58 and 32%. Results are presented in table 3 and 10.

9.4.2. Acute invasive aspergillosis (caused by *Aspergillus* spp)

- Mortality without antifungal treatment is 100%; 40% respond to itraconazole treatment. Over 50% respond to voriconazole, the internationally recommended first line treatment (table 4 and 10).

9.4.3. Disseminated histoplasmosis

- >80% in non-immunocompromised patients compared with 63% for 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 (table 5).

9.4.4. Sporotrichosis

- >90% response rate over 3-6 months, much superior to potassium iodide and fluconazole but equivalent to terbinafine (table 6).

9.4.5. Paracoccidioidomycosis

- >85% response rates, with a faster response time than sulphadiazine or cotrimoxazole (table 7).

9.4.6. Systemic Mycoses due to *Talaromyces marneffei* infection

- 97% response rate to amphotericin B followed by itraconazole (table 8).

9.4.7. Chromoblastomycosis (Chromo)

- ~40% response rates (table 9).

10. Review of benefits: summary of comparative effectiveness in a variety of clinical settings

10.1. 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.

10.2. Summary of available data for itraconazole

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

Itraconazole was developed between 1985 and 1991. A randomised study comparing intravenous conventional amphotericin B and oral itraconazole in the USA failed to enrol and was terminated, but as itraconazole was the first oral agent with efficacy for invasive aspergillosis, the FDA and European authorities approved its use based on prospective open label single arm studies. Likewise, it was deemed impossible to recruit patients to randomised studies of histoplasmosis and sporotrichosis. Randomised studies have been conducted *T. marneffei* infection in AIDS, chronic pulmonary aspergillosis and paracoccidioidomycosis, as well as allergic bronchopulmonary aspergillosis, for the prevention of invasive aspergillosis in leukaemia and dermatophytosis, none the focus of this application.

10.2.1. Summary of available estimates of comparative effectiveness for itraconazole

The outcomes of the many studies are summarised in the following tables. Endpoints for chronic pulmonary aspergillosis are challenging for several reasons, but mostly because radiology improvement and *Aspergillus* IgG and inflammatory markers change slowly (over many months or years).

Table 3. Effectiveness of itraconazole in clinical trials of chronic pulmonary aspergillosis

Disease	References	Type of study	Number of patients	Treatment	Outcome
Chronic Pulmonary Aspergillosis	(37)	Prospective, multicentre, uncontrolled	28 patients (14 aspergilloma and 14 chronic pulmonary aspergillosis)	Itraconazole 200-400mg daily for 2-16 months	In aspergilloma, 2 cures and 8 improvements (71%). In chronic necrotising pulmonary aspergillosis, 13 improved (93%) and 3 (23%) relapsed.
	(38)	Prospective, multicentre, uncontrolled	29 patients enrolled, safety in 24 and efficacy in 23	Intravenous and then oral itraconazole. Usually 2 weeks IV. Oral dose was 400mg/d. Mean duration of therapy 52 days (± 34).	Of the 23 patients, 10 (43.5 %) responded. With respect to the administration period, the response rates in 8 patients treated for a short period and 15 treated for a long period were 25.0 % and 53.3 %, respectively
	(39)	Prospective, randomised open, single-centre study	17 patients itraconazole group vs 14 in control group	Itraconazole (400 mg/day for 6 months) vs standard supportive therapy	Response of 76.5% in itraconazole group vs 35.7% in control group (p=0.02). 30% relapsed in the 6 months after therapy in the itraconazole group.

Table 4. Effectiveness of itraconazole in clinical trials of acute invasive aspergillosis

Disease	References	Type of study	No patients	Treatments	Outcome
Acute invasive aspergillosis	(40)	Compassionate use, prospective uncontrolled.	125	It was difficult to analyse the effect of itraconazole dose because (1) the patients were enrolled over an extensive period, during which the dose of itraconazole was being increased on entry and in patients already receiving therapy as more safety information became available; (2) doses were given in 50- to 100-mg increments regardless of the patient's weight; and (3) individual patients had dose changes during the study because of an impression of insufficient response.	34 (27%) had a complete response, 45 (36%) improved, 20 (16%) were unchanged, and 26 (21%) worsened. The subset receiving less than 2 weeks of itraconazole therapy had a worse outcome than the remainder of the group as did patients with sinus, central nervous system, or widely disseminated disease
	(41)	Multicentre prospective, uncontrolled study in patients with various underlying conditions.	76 evaluable	Itraconazole (600 mg/day for 4 days followed by 400 mg/day)	At the end of treatment, 30 (39%) patients had a complete or partial response and 3 (4%) had a stable response. In 20 patients (26%), itraconazole was discontinued early (at 0.6 to 54.3 weeks) because of a worsening clinical course or death due to aspergillosis (itraconazole failure). 23 (30%) patients withdrew for other reasons including toxicity (7%) and death due to another cause but without resolution of aspergillosis (20%).

Table 5. Effectiveness of itraconazole in clinical trials of histoplasmosis.

Disease	References	Type of study	No patients	Treatments	Outcome
Histoplasmosis	(42)	Prospective, , multicentre uncontrolled	37 patients with culture or histopathologic evidence	Itraconazole 200-400 mg/day	Success was defined as either cure (2 months of therapy and resolution or reduction of symptoms and/or >50% reduction of radiology abnormality and negative cultures or clinical response and negative cultures (for protocol violating patients). Success was documented in 30 patients (81%) out of 37. The success rate for patients treated for more than 2 months was 86%. All failures occurred in chronic cavitary pulmonary disease.
	(43)	Multicentre, uncontrolled, prospective trial in AIDS patients with mild disseminated histoplasmosis	59 patients	Itraconazole oral 300/12h mg for 3 days and then 200 mg/12h for 12 weeks.	Success was documented in 50 (85%) out of 59 evaluable patients.
	(44)	Prospective, randomized, double-blind, placebo-controlled prophylaxis trial	295 patients with CD4 counts <150/mm^3 residing in a histoplasmosis endemic area	Itraconazole capsules 200mg daily vs placebo	Histoplasmosis developed in 4 (2.7%) of itraconazole group vs 10 (6.8%) of placebo (p=0.03). In general, 29 (19.5%) patients developed a fungal opportunistic infection in itraconazole group vs 42 (28.8%) in placebo. (p=0.004). Prophylaxis significantly decreased the incidence of histoplasmosis (p= 0.02; log-rank test) and all invasive fungal infections (p=0.0009; log-rank test) in patients with CD4 counts <100/ mm^3.

Table 6. Effectiveness of itraconazole in clinical trials of sporotrichosis

Disease	References	Type of study	No patients	Treatments	Outcome
Sporotrichosis	(45)	Prospective, uncontrolled, multi-centre, including compassionate use.	27 patients with cutaneous and systemic sporotrichosis were treated with 30 courses of itraconazole	Patients received from 100 to 600 mg of itraconazole daily for 3 to 18 months	Among the 30 courses there were 25 (83.3%) responders and 5 non responders.
	(46)	Prospective, uncontrolled, multi-centre, study with diagnosis by means of isolation of fungi in culture	17 patients with cutaneous and lymphangitic sporotrichosis	Itraconazole 100 mg/day for 90-180 days	100% response
	(47)	Prospective, uncontrolled, multi-centre, study with diagnosis by means of isolation of fungi in culture	18 adult white male patients with cutaneous sporotrichosis	Itraconazole in different daily dose schemes (100-200 mg/day)	100% response

Table 7. Effectiveness of itraconazole in clinical trials of paracoccidioidomycosis

Disease	References	Type of study	No patients	Treatments	Outcome
Paracoccidioidomycosis	(48)	Retrospective, partially controlled cohort study of proven infections seen between 1993 to 2009	81 patients treated with itraconazole and 119 with TMP-SMX	Oral itraconazole, 200 mg/d for 6 to 9 months, was used for mild disease and 200 mg/d for 12 to 18 months for moderate disease vs TMP-SMX 480/2400 mg/d for 12 months in mild cases and for 24 months in moderate cases	Itraconazole response was 86.4% vs 51.3% with TMP-SMX (12 months treatment with itraconazole vs 23 months with TMP-SMX to get response). The Cox proportional hazard regression model showed that use of itraconazole increased the hazard of cure compared with the use of the TMP–SMX

Table 8. Effectiveness of itraconazole in clinical trials of systemic mycoses caused by *Talaromyces marneffei*

Disease	References	Type of study	No patients	Treatments	Outcome
Systemic mycoses caused by *Talaromyces marneffei*	(49)	Prospective, double-blind, placebo-controlled trial for prophylaxis	63 patients with HIV infection and CD4+ lymphocyte counts of <200 cells/µL were randomized to receive oral itraconazole and 66 similar patients received a matched placebo.	200 mg oral itraconazole vs placebo	In the intent-to-treat analysis, a systemic fungal infection developed in 1 patient (1.6%) in the itraconazole group (*T. marneffei*) and in 11 patients (16.7%) receiving placebo (7 patients had cryptococcal meningitis, and 4 patients had *T. marneffei* infection; P=0.003, by the log-rank test)
	(50)	Prospective, uncontrolled, multi-centre	74 HIV-infected patients with disseminated *T. marneffei* infection, diagnosed by positive fungal culture and clinical evidence of infection	Amphotericin B at a dosage of 0.6 mg/kg/day IV for 2 weeks, followed by a 400-mg/day of oral itraconazole for 10 weeks	72 (97.3%) responded to the treatment

Table 9. Effectiveness of itraconazole in clinical trials of chromoblastomycosis

Disease	References	Type of study	No patients	Treatments	Outcome
Chromoblastomycosis	(51)	Prospective, uncontrolled, multi-centre of cases diagnosed by direct mycological examination, culture, and histopathology	19 patients with histopathologically and mycologically proven active chromoblastomycosis due to *Fonsecaea pedrosoi*	Oral itraconazole 200-400 mg/day	Eight patients (42%) having mild to moderate disease were clinically and biologically cured after a mean duration of therapy of 7.2 months (3.2-29.6 months). Clinical improvement was obtained in 4 patients (21%) with severe lesions after a mean treatment time of 17.6 months (10.7-22.5 months). In total, 12 (63%) out 19 patients benefited from the treatment.
	(52)	Prospective, uncontrolled, single-centre study with diagnosis by direct mycological examination, culture, and histopathology	10 patients with active chromoblastomycosis due to *F. pedrosoi*	Oral itraconazole 100 or 200 mg/day for 12-24 months	3 patients had minor category, 5 moderate and 3 severe. One patient with severe lesions was lost in the follow up. At 12 months of treatment 2 patients were cured, 3 had major improvement and 4 minor improvement. In total, 9 (90%) of the 10 patients benefited from the treatment.

Oral capsules and solution of itraconazole are approved by international agencies for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non- meningeal histoplasmosis, and;
- Invasive aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

More details are provided in section 13 “Summary of regulatory status of the medicine”.

In addition, itraconazole has been also recommended in different guidelines as table 12 and 13 show. The methodology used to establish the quality of the evidence in the guidelines is explained below in figure 1 and table 11 respectively.

10.3. Summary of available data for voriconazole

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

Voriconazole was first used in clinical trials in 1993 and the first patients were enrolled in Manchester and then Europe (53, 54). Planning for 2 large Phase 3 studies of voriconazole started in 1997, and the studies were completed and merged for analysis in 2001 (55). The Phase 2 intravenous dose of 3mg/Kg (after loading) was elevated to 4mg/Kg for the randomised studies. The comparator for the randomised studies was conventional amphotericin B, as this was the only licensed agent for invasive aspergillosis with the FDA. During and subsequent to the randomised studies lipid-associated amphotericin B became available, which is less toxic, but no more efficacious for invasive aspergillosis. In this application, we have relied on the single, powerful randomised study publication (56), and support it with several subsequent ‘real-life’ published experiences also indicating the superiority of voriconazole over all other agents.

10.3.1. Summary of available estimates of comparative effectiveness for voriconazole

The outcomes of the prospective studies in invasive and chronic pulmonary aspergillosis are summarised table 10. Endpoints for chronic pulmonary aspergillosis are challenging for several reasons, but mostly because radiology improvement and *Aspergillus* IgG and inflammatory markers change slowly (over many months or years). We have excluded the short term, IV voriconazole only randomised study of chronic pulmonary aspergillosis (57), because IV voriconazole is rarely used for this indication and one month is too short a period to assess response.

Table 10. Effectiveness of voriconazole in clinical trials

Disease	References	Type of study	No patients	Treatments	Outcome
Chronic pulmonary aspergillosis	(58)	Prospective, open, multicentre trial for efficacy and safety of voriconazole	41	Voriconazole (200 mg twice daily) for a period of 6–12 months and were followed for 6 months after the end of therapy	32% of success at 6 months; 53 % for chronic necrotizing aspergillosis and 14 % for chronic cavitary aspergillosis. The respective success rates at end of therapy were 58 and 32 %.
Acute invasive aspergillosis	(56, 59)	Two randomised, open, multicentre studies with identical enrolment and evaluation criteria, identical therapies, but different primary endpoints. All evaluations were done by an external blinded (to therapy) group of radiologists and clinicians.	391 enrolled, 277 included in the final analysis (with invasive aspergillosis)	Intravenous voriconazole, 6mg/Kg 12 hourly loading dose, followed by 4mg/Kg 12 hourly versus amphotericin B deoxycholate 1mg/Kg initially. In both arms, a switch for toxicity or clinical failure was allowed to 'other licensed antifungal therapy' (OLAT), which was lipid-associated amphotericin B or oral itraconazole.	Of the 391 patients enrolled, 102 did not have invasive aspergillosis, and 12 did not receive any therapy. 76 of 144 (53%) responded to voriconazole compared to 42 of 133 (32%) who responded to amphotericin B. At 12 weeks, survival with voriconazole was 71% versus 58% with amphotericin B. 52 (36%) of patients on voriconazole switched to OLAT, compared with 107 (80%) on amphotericin B. Of the 26 patients who were treated with 12 weeks of amphotericin B deoxycholate, 1 (4%) responded.

Voriconazole is approved in most countries in the world for the initial treatment of invasive aspergillosis and recommended as first line therapy for invasive aspergillosis in all national and international guidelines. It is also recommended as first and second line therapy for chronic pulmonary aspergillosis in European and IDSA guidelines.

More details are provided in section 13 “Summary of regulatory status of the medicine”.

In addition, voriconazole has been also recommended in different guidelines as table 14 shows. The methodology used to establish the quality of the evidence in the guidelines is explained below in figure 1 and table 11 respectively.

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology (unrestricted use of the figure granted by the US GRADE Network (60).

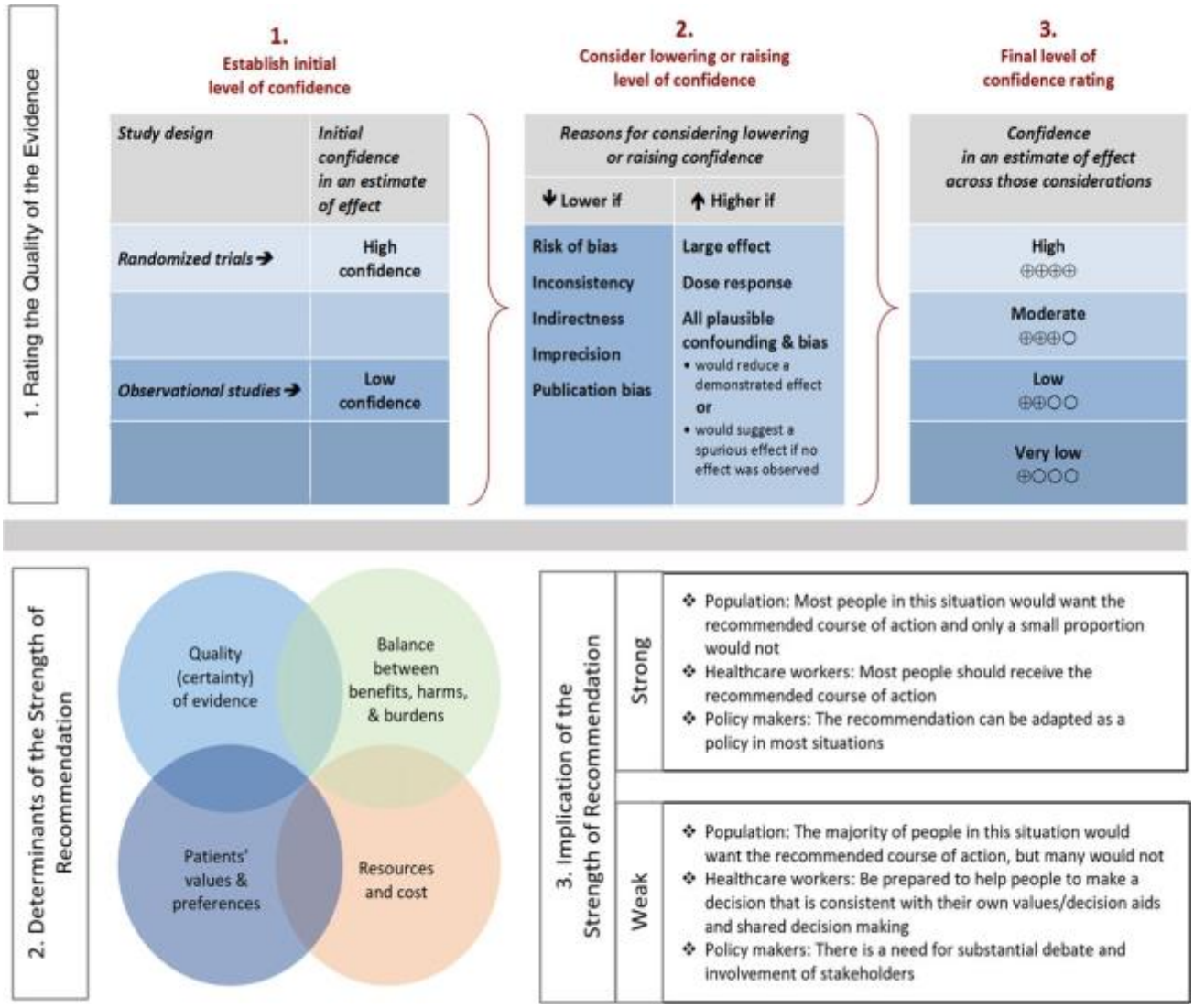

Table 11. Strength and quality of evidence recommendation for non-GRADE methodologies (61)

Strength of recommendation	A	Good evidence to support a recommendation for use.
	B	Moderate evidence to support a recommendation for use
	C	Poor evidence to support a recommendation
Quality of evidence	I	Evidence from 1 properly randomized, controlled trial. Experiments.
	II	Evidence from 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled
	III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Table 12. Itraconazole recommendations in guidelines

Disease	Reference	Methodology	Quality of evidence & Recommendation	Doses	Comments
Invasive aspergillosis	(5)	GRADE (figure 1)	Moderate & weak	Itraconazole suspension, 200 mg/12h as salvage therapy (not graded in the 2016 IDSA guidelines).	Voriconazole is the recommended treatment for this condition. Itraconazole is useful for patients who cannot take IV therapy, and are intolerant of voriconazole.
Chronic pulmonary aspergillosis	(5)	GRADE (figure 1)	High quality & Strong	Itraconazole capsules or oral solution, 200 mg/12h.	Voriconazole is also used for this indication.
Histoplasmosis	(62)	Canadian Task Force on the Periodic Health Examination (table11) (61)	Depending of the clinical picture recommendations are AI, AII and BIII.	Itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily).	Itraconazole given orally is preferred for patients who have mild-to-moderate histoplasmosis as stepdown therapy after the initial response to amphotericin B. The response rate for primary therapy with itraconazole in early studies was 100% for disseminated histoplasmosis and 80% for pulmonary histoplasmosis. The oral capsule formulation or the solution can be used.

Sporotrichosis	(63)	Canadian Task Force on the Periodic Health Examination (table 11) (61)	B-III	Itraconazole 200 mg/day or 200 mg/12h for mild disease. For pulmonary, meningitis and disseminated, liposomal amphotericin B.	For cutaneous and lymphocutaneous infections, response rates of 90%–100% were noted with itraconazole therapy, compared with a 63%–71% response rate associated with fluconazole therapy.
Systemic mycoses caused by *Talaromyces marneffei*	(64)	Similar to Canadian Task Force on the Periodic Health Examination (table 11) (61)	AII to BII	The recommended treatment is liposomal amphotericin B, 3 to 5 mg/kg body weight/day intravenously for 2 weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks (AII), followed by secondary prophylaxis. Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks (BII), followed by 200 mg/day for prevention of recurrence.	

Table 13. Itraconazole recommendation in guidelines for children

Disease	Reference	Methodology	Quality of evidence & Recommendation	Recommendation
Sporotrichosis	(63)	Canadian Task Force on the Periodic Health Examination (table 11)(61)	BIII	Itraconazole 6–10 mg/kg/day (400 mg/day maximum) for mild disease (B-III); deoxycholate amphotericin B 0.7 mg/kg/day for severe disease (B-III).
Histoplasmosis	(62)	Canadian Task Force on the Periodic Health Examination (table 11) (61)	AIII	Itraconazole dosage in children is 5.0–10.0 mg/kg daily in 2 divided doses (not to exceed 400 mg daily), generally using the solution formulation (A-III).

Table 14. Voriconazole recommendation in guidelines

Disease	Reference	Methodology	Quality of evidence & Recommendation	Comments
Invasive aspergillosis in adults	(5)	GRADE (figure 1)	Strong recommendation; high-quality evidence	Voriconazole in adults is loaded at 6 mg/kg/dose twice daily, followed by 4 mg/kg/dose twice daily; Early initiation of antifungal therapy in patients with strongly suspected invasive aspergillosis is warranted while a diagnostic evaluation is conducted (strong recommendation; high-quality evidence); The treatment of invasive aspergillosis must be continued for a minimum of 6–12 weeks, largely dependent on the degree and duration of immunosuppression, site of disease, and evidence of disease improvement (strong recommendation; low quality evidence); For patients with successfully treated invasive aspergillosis who require subsequent immunosuppression, secondary prophylaxis should be initiated to prevent recurrence (strong recommendation; moderate-quality evidence).
Invasive aspergillosis in children	(5)	GRADE (figure 1)	Strong recommendation; high-quality evidence	Voriconazole is recommended as the choice treatment of aspergillosis in all ages children although the dosing is different (intravenous loading dose of 9 mg/kg twice daily. Maintenance intravenous dosing is 8 mg/kg/dose. Oral dosing must be of 9 mg/kg/ dose;
Chronic pulmonary aspergillosis	(5, 65)	GRADE (figure 1) and ESCMID*	Strong recommendation; high-quality evidence; AII	Based on a mixture of prospective studies and case series, with different measures of success including clinical improvement, radiological improvement, negativisation of *Aspergillus* cultures and quality of life improvement.

* ESCMID assessment of quality of evidence and recommendation are described by Ullman et al (66).

11. Reviews of harms and toxicity: summary of evidence on safety

11.1. Itraconazole

11.1.1. 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 chronic pulmonary aspergillosis, invasive aspergillosis, sporotrichosis, histoplasmosis, paracoccidioidomycosis, *T. marneffei* infections and chromoblastomycosis. Other infections that have been also treated with itraconazole are vaginal thrush, oropharyngeal and oesophageal candidiasis, fungal skin infections, allergic bronchopulmonary aspergillosis, cryptococcosis, blastomycosis, coccidioidomycosis, and systemic candidiasis. Millions of patients have received treatment.

11.1.2. Description of the adverse effects/reactions and estimates of their frequency

The usual treatment doses (i.e. $\leq$ 200mg daily) have a low side effect profile. In common with most medicines, adverse events become more common at higher doses ($\geq$ 400mg daily).

Immediate adverse events

The most common are gastro-intestinal side effects, particularly in neutropenic and HSCT 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.

Short term adverse events

Ankle oedema is relatively common in older people taking itraconazole for several weeks, occasionally associated with congestive cardiac failure. Mild hypertension is seen in some patients. Hypokalaemia with weakness may occur, as may general

fatigue. Hypokalaemia and renal impairment are much less frequently than with amphotericin B. Sleep disturbance is uncommon. Nausea, vomiting and especially diarrhoea are more common with oral solution compared with capsules.

Long term adverse events

Once patients have been taking itraconazole for >3 months, liver function abnormalities are very uncommon. Peripheral neuropathy, seen with itraconazole, may be more common than for fluconazole, and probably more common than for voriconazole and posaconazole. Erectile dysfunction has also been reported.

Table 15. Data published between 1987 to 2008 about frequency of adverse effects with itraconazole (Lestner and Denning, unpublished literature review)

Adverse effect	Cumulative data	%
	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

11.1.3. Drug-Drug Interactions

Itraconazole's tolerability profile is acceptable, but drug/drug interactions require care in prescribing it, notably with some anti-retrovirals (ARVs) and rifampicin (67).

Drug-drug interactions 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. Itraconazole metabolism is accelerated by concomitant administration of rifampicin, phenytoin and carbamazepine, which potentially results in an inability to achieve therapeutic serum concentrations (68). 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 syndrome of inappropriate ADH secretion (SIADH) (69). Itraconazole also prolongs the action of midazolam, digoxin, cyclosporine, tacrolimus, sirolimus, statins and warfarin (70-73).

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, Nevirapine, Maraviroc. NNRTIs are the biggest problem (74).

11.1.4. 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, e.g. QT prolongation, congestive cardiac failure, ankle oedema and hypertension.

11.2. Voriconazole

11.2.1. Estimate of total patient exposure to date

Voriconazole has been used across the world since first licensure in 2002. Millions of patients have been treated, including many 100,000's of children. It is licensed in 100 countries, including all high income countries, the most populous countries of India, China, Brazil, Indonesia, the Philippines, Egypt, Nigeria, Mexico, Thailand but not Bangladesh, DRC or Ethiopia. Generic voriconazole is available in Pakistan, and probably many other countries.

11.2.2. Description of the adverse effects/reactions and estimates of their frequency

The profile of adverse reactions to voriconazole includes transient visual disturbances (characterized principally by photopsia); hepatotoxicity, which may be dose limiting (manifested by elevated serum bilirubin, alkaline phosphatase, and hepatic aminotransferase enzyme levels); skin rash, erythroderma, photosensitivity, cheilitis,

and perioral excoriations; nausea, vomiting, and diarrhoea; visual or auditory hallucinations; and cardiovascular events including tachyarrhythmias and QT interval prolongations on electrocardiography. There have also been rare cases of arrhythmia (including ventricular arrhythmias such as torsade de pointes and bradycardia), cardiac arrest, and sudden death in patients taking voriconazole, probably related to excessive plasma concentrations. These cases usually involve patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia, and concomitant medications (e.g., quinolones) that may be contributory. Visual side effects or photopsia are self-limited, reversible, and not clearly associated with absolute drug levels. Mild hepatotoxicity is common as for all azoles and related to drug concentration. Severe hepatotoxicity is uncommon. Reversible central and peripheral neurologic symptoms and hallucinations may be observed in association with higher drug concentrations but with significant variability; these may be confused with other aetiologies of CNS dysfunction including posterior reversible leukoencephalopathy syndrome or calcineurin inhibitor toxicity. Voriconazole concentrations may be a predictor of CNS neurotoxicity, which is reversible. The use of prolonged voriconazole therapy (as for osteomyelitis or meningitis) or prophylaxis has revealed newer toxicities including periostitis with severe pain in bones or joints in association with elevated serum fluoride levels. The risk for squamous cell skin cancer or melanoma in sun-exposed areas is enhanced by concomitant immunosuppression and chronic voriconazole use, especially in fair-skinned persons (5). As with itraconazole, peripheral neuropathy may occur after months of therapy, usually sensory, sometimes motor or mixed, and is related to increased doses required to achieve adequate plasma concentrations.

11.2.3. Drug-Drug Interactions

There is an extensive list of drug-drug interactions with voriconazole because it is metabolised by CYP3A4, 2C9 and 2C19 pathways. Voriconazole´s tolerability profile is acceptable, but drug/drug interactions require care in prescribing it, notably with some anti-retrovirals (ARVs) and rifampicin. Voriconazole metabolism is accelerated by concomitant administration of rifampicin, phenytoin, carbamazepine and St John’s Wort, which potentially results in an inability to achieve therapeutic serum

concentrations. In addition, many clinically significant interactions relate to the suppression of CYP3A4 activity by the action of midazolam, cyclosporine, tacrolimus, sirolimus, some statins and warfarin. In HIV infected patients there are important interactions with antiretrovirals. There are potential moderate or severe interactions with the following antiretrovirals: atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, tipranavir, delavirdine, efavirenz, nevirapine, maraviroc. Prolongation of QTc interval may follow co-administration with astemizole, cisapride, pimozide, quinidine and terfenadine. Increased exposure to alfentanil, fentanyl, oxycodone and methadone may be problematic and lead to respiratory depression or prolonged anaesthetic effect. Omeprazole and related compounds increase voriconazole concentrations in proportion to dose, which is used as an inexpensive means of increasing voriconazole plasma levels in those with sub therapeutic levels. A modest effect to raise oral hypoglycaemic agent levels (tolbutamide, glipizide and glyburide) is likely, with the possibility of hypoglycaemia. Prednisolone exposure is increased by about 30% by voriconazole (67).

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

The extremes of age are more likely to have sub-therapeutic (children) or toxic (older people) levels and exposures. We have conducted an internet based international survey of TDM capacity and few countries have voriconazole TDM capability. Seventy-eight respondents from 33 countries completed a questionnaire, including 4 countries in Africa. Voriconazole TDM is available throughout most of western Europe, the USA, Australasia, South Korea, India, Brazil, Venezuela and Indonesia. We found no evidence of TDM in China or Japan, but we believe some centres offer it.

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

12.1. 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 and Sri Lanka to $102.00 in Sweden, with a median daily 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.

As generic voriconazole is only just being introduced, prices are changing rapidly in many countries, but are generally quite high. For example, a day of treatment with oral voriconazole in Thailand costs $94.00, in Venezuela $33.08, in Uganda costs $22.86, whereas in Pakistan generic voriconazole would cost $2.08 per day.

12.2. 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.

12.2.1. 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 with itraconazole 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 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" (75). This is a realistic scenario, where the risk of disseminated histoplasmosis is high, and in the Guiana Shield, some Central American countries and certain localities in South America.

12.2.2 Therapy for invasive aspergillosis with voriconazole

Numerous cost-effectiveness studies have been published for voriconazole, generally showing that successful therapy is less expensive than unsuccessful and more toxic therapy with amphotericin B. However, these are mostly out of date now as they related to premium pricing of the drug. All are in high income countries where the cost of hospitalisation is very high, as is the development of renal failure with amphotericin B. We have not included these here.

13.Summary of regulatory status of the medicine

13.1. US Food and Drug Administration

Itraconazole capsules are indicated 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;
- Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Voriconazole is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

- Invasive aspergillosis;
- Candidaemia in non-neutropenic patients;
- Disseminated *Candida* infections in skin and infections in abdomen, kidney, bladder wall, and wounds;
- Oesophageal candidiasis;
- Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy.

13.2. European Medicines Agency

Itraconazole capsules are indicated for:

- Vulvovaginal candidosis;

- Pityriasis versicolor;
- Dermatophytoses caused by organisms susceptible to itraconazole (*Trichophyton* spp., *Microsporum* spp., *Epidermophyton floccosum*), e.g., tinea pedis, tinea cruris, tinea corporis, tinea manuum;
- Oropharyngeal candidosis;
- Onychomycosis caused by dermatophytes and/or yeasts;
- The treatment of histoplasmosis;
- Itraconazole is indicated in the following systemic fungal conditions when first-line systemic anti-fungal therapy is inappropriate or has proved ineffective. This may be due to underlying pathology, insensitivity of the pathogen or drug toxicity:
    - Treatment of aspergillosis and candidosis;
    - Treatment of cryptococcosis (including cryptococcal meningitis): in immunocompromised patients with cryptococcosis and in all patients with cryptococcosis of the central nervous system;
    - Maintenance therapy in AIDS patients to prevent relapse of underlying fungal infection.
- Itraconazole is also indicated in the prevention of fungal infection during prolonged neutropenia when standard therapy is considered inappropriate.

Voriconazole is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients in adults and children over the age of two years:

- Invasive aspergillosis;
- Candidaemia in non-neutropenic patients;
- Serious invasive *Candida* infections when the fungus is resistant to fluconazole;
- Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy.

13.3. Australian Government, Department of Health, Therapeutic Goods Administration

Itraconazole capsules are indicated for the treatment of the following fungal infections:

- Systemic aspergillosis;
- Histoplasmosis;
- Sporotrichosis;
- Treatment and maintenance therapy in AIDS patients with disseminated or chronic pulmonary histoplasmosis infection.

Voriconazole is indicated for the treatment of the following fungal infections:

- Invasive aspergillosis;
- Serious *Candida* infections (including *C. krusei*), including oesophageal and systemic *Candida* infections (hepatosplenic candidiasis, disseminated candidiasis, candidaemia);
- Serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp;
- Other serious fungal infections, in patients intolerant of, or refractory to, other therapy;
- Prophylaxis in patients who are at high risk of developing invasive fungal infections.

Itraconazole is available and approved in most countries but its availability in about 30 countries is uncertain. Itraconazole is not registered or available in Cameroon, Eritrea, Gambia and Senegal, and is registered but not available in the Dominican Republic, Ghana or Ukraine. At least 152 million people have no access to itraconazole.

Voriconazole is licensed in at least 100 countries. Generic voriconazole is now becoming available in many countries. GAFFI is in the middle of an exercise to document availability and price, but this is not yet concluded.

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopeia, European 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
- https://www.drugs.com/pro/voriconazole.html

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