Section 6. 3

Application to move amphotericin B deoxycholate from the complimentary list to core list

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Application for WHO Model List of Essential Medicines: *Amphotericin B*

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

This is a proposal for inclusion of 'amphotericin B deoxycholate' as a WHO Essential Medication, effectively moving amphotericin B deoxycholate from the *complimentary list* to the *essential list*. Cryptococcal meningitis is the most common cause of meningitis in adults in sub-Saharan Africa and accounts for 20-25% of AIDS-related mortality [1]

The principal reasons for requesting the inclusion of Amphotericin B in the WHO essential list are as follows:

- Current cryptococcal meningitis mortality rates with fluconazole monotherapy are unacceptably high (≥60% 10-week mortality). Amphotericin B therapy, when compared to fluconazole monotherapy, provides a 25-30% improved 10-week survival [2].
- All current cryptococcal meningitis guidelines, including the 2011 WHO rapid advice for the diagnosis, prevention, and management of cryptococcal disease, recommend AmB-based antifungal regimens as first line therapy [3].

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

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3. Name of the organizations consulted and/or supporting the application

Centers for Disease Control and Prevention, USA
St. George's University of London, UK
Médecins Sans Frontières
Clinton Health Access Initiative (CHAI)
University of Minnesota, USA
Management Sciences for Health, USA
National Institute for Communicable Diseases, South Africa

4. International Nonproprietary Name (INN, generic name) of the medicine

Amphotericin B deoxycholate

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Intravenous

6. International availability - sources, if possible manufacturers and trade names:

Amphotericin B deoxycholate (Fungizone™) was originally manufactured by Bristol-Meyers Squibb; however, multiple generic manufacturers exist in every region. (Table 1) X-Gen Pharmaceuticals (US) manufacturers the only FDA approved generic formulation of amphotericin B, as listed in the 2012 version of the Orange Book (www.accessdata.fda.gov).

Table 1. Amphotericin B manufacturers and trade names

No.	Trade Name(s)	Manufacturer, Country
1.	Fungizone	Bristol-Meyers Squibb
2.	Amfotex	Alkem Laboratories Ltd (Cytomed), India
3.	Amphotret	Bharat Serum & Vaccines Ltd, India; Xeno Pharmaceuticals, Philippines
4.	Phoricin	Chandra Bhagat Pharma Pvt Ltd, India
5.	Amfocare, Amphocil	Criticare Laboratories Pvt. Ltd. , India
6.	Amfocan	Dabur Pharmaceuticals Ltd., India
7.	Fungitericin	Lifecare Innovations Pvt. Ltd., India
8.	Fungizone Intravenous	Nicholas Piramal India Ltd. , India
9.	Mycol	V.H. Bhagat Pharmaceuticals Pvt. Ltd., India
10.	Amphotericin B	Taj Pharmaceuticals Ltd., India
11.	Anfotericina B	BestPharma, Peru
12.	Anfotericina B	Biosano, Chile
13.	Anfotericina B	Northia, Argentina
14.	Anfotericina	Fada, Argentina
15.	Anfotericina	Richet, Argentina
16.	Anfotericina B	Richet (Dominican Republic, Guatemala, Honduras, Panama, Venezuela)
17.	Fengkesong	Asia Pioneer, China; Shanghai Pharma Group, China
18.	Ampholin	Mediorals, Thailand
19.	Amphotericin B Biolab	Biolab, Thailand
20.	Amphotericin B Asence	Asence, Thailand
21.	Halizon	Fuji Yakuhin, Japan
22.	Amphotericin B	Dumex, Ethiopia
23.	Amphotericin B	Sintez, Russia
24.	Amphotericin B	Abbott Laboratories, APP Pharmaceuticals, Pharma Tek, Sicor Pharmaceuticals, X-Gen, USA

7. Whether listing is requested as an individual medicine or as a therapeutic group

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

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population):

Cryptococcal meningitis is the most common cause of meningitis in sub-Saharan Africa [4-6], accounting for 20-25% of AIDS-related mortality in Africa and causing an estimated 500,000 deaths annually [1]. In meningitis surveillance studies from South Africa, Malawi, and Uganda, cryptococcal meningitis is more common in adults than all causes of

bacterial meningitis combined [4-6]. Cryptococcosis primarily occurs among HIV-infected persons living with AIDS, predominantly when CD4 T cell counts are < 100 cells/mcL.

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

Amphotericin B deoxycholate dosed at 0.7-1.0 mg/kg/day for 1-2 weeks is the standard induction therapy as recommended by the WHO [3], South African HIV Clinicians Society [7], Infectious Disease Society of America [8], and U.S. Department of Health and Human Services [9]. (Table 2) (Figures 1 & 2) WHO recommendations for children are the same as for adults but with weight based dosing regimens.

Table 2. WHO, IDSA & South African HIV Clinician Society Guidelines for the induction treatment of CM depending on the clinical setting

Clinical setting for treatment of cryptococcal meningitis		**WHO 2011 Rapid Guidelines [3]**	**IDSA 2010 Guidelines [8]**	**South African HIV Clinician Society 2007 guidelines [7]**
Amphotericin B deoxycholate (AmBd)	**5FC**			
Accessible Facilities for toxicity management* available	Accessible	AmBd (0.7-1 mg/kg/day) **+** 5-FC (100 mg/kg/day)	AmBd (0.7–1.0 mg/kg/day) + 5-FC (100 mg/kg/day) *or* Liposomal AmB (3–4 mg/kg/day) *or* ABLC (5 mg/kg/day) + 5-FC (100 mg/kg/day)	Not applicable-5-FC currently unavailable in SA
Accessible Facilities for toxicity management* available	Not accessible	AmBd (0.7-1 mg/kg/day) **+** Fluconazole (800 mg/day)	AmBd (0.7–1.0 mg/kg/day) *or* liposomal AmB (3–4 mg/kg/day) *or* ABLC (5 mg/kg/day) *or* AmBd plus fluconazole	AmBd (1 mg/kg/day) IV For 2 weeks (minimum 1 week)
Accessible Facilities for toxicity management* limited	Not accessible	AmBd (0.7-1 mg/kg/day) For 5-7 day**s +**Fluconazole (800 mg/day) For 2 weeks	Scenario not addressed	AmBd (1mg/kg/day) Minimum 1 week
Not accessible	Accessible	Fluconazole (1200 mg/day) **+** 5-FC (100 mg/kg/day) For $\geq$ 2 weeks	Fluconazole (800 – 1200(favoured) mg/day)**+** 5-FC (100 mg/kg/day orally) For 6 weeks	Not applicable-5-FC currently unavailable in SA
Not accessible Facilities for toxicity management* not available	Not accessible	Fluconazole (1200 mg/day) For $\geq$2 weeks	Fluconazole (800–2000 mg/day) For 10–12 weeks (Fluconazole 1200 mg/day favoured)	Transfer patient to centre where AmBd available. If not possible, Fluconazole (800mg/day) For 4 weeks

All induction CM courses are for 2 weeks' duration, unless stated

*Minimum package of pre-hydration, electrolyte replacement and toxicity monitoring/management available

Figure 1. WHO Rapid Advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children (Dec 2011): Text description [3] (http://www.who.int/hiv/pub/cryptococcal_disease2011/en/)

Summary of induction, consolidation and maintenance treatment recommendations and dosage for HIV-infected adults, adolescents and children (See Table 1)

1. Induction phase treatment

For the induction phase of treatment in HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal), the following two-week anti-fungal regimens are recommended in order of preference.

a. Amphotericin B + flucytosine
   [Strong recommendation, high quality of evidence]

b. Amphotericin B + fluconazole
   [Strong recommendation, moderate quality of evidence]

c. Amphotericin B short course (5-7 days) + high-dose fluconazole (to complete two weeks of induction) when a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management cannot be provided for the full two week induction period.
   [Conditional recommendation, low quality of evidence]

d. Fluconazole high dose + flucytosine, when amphotericin B is not available
   [Conditional recommendation, low quality of evidence]

e. Fluconazole high dose alone, when amphotericin B is not available
   [Conditional recommendation, low quality of evidence]

Figure 2. WHO Rapid Advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents & children (Dec 2011): Table summary [3]

Drugs available	Pre-hydration + electrolyte replacement + toxicity monitoring/ management	Induction phase options[14] (2 weeks)	Consolidation phase options (8 weeks)	Maintenance/ secondary prophylaxis options
Amphotericin B[15] ± flucytosine	Available	**a.** Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day **b.** Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day	Fluconazole 400-800 mg/day	Fluconazole 200 mg daily
Amphotericin B[15]	Not available for full 2 week induction period	Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 800 mg/day (2 weeks)	Fluconazole 800 mg/day	
Amphotericin B not available	Not available	**a.** Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day **b.** Fluconazole 1200 mg/day alone	Fluconazole 800 mg/day	

10. Summary of comparative effectiveness in a variety of clinical settings

• ***Identification of clinical evidence*** (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

In 2012, a systematic review assessed the cost-effectiveness of cryptococcal treatment outcomes in resource-limited settings [2]. In brief, Rajasingham et al [2] performed a MESH search of "Cryptococcal Meningitis" AND "Therapy", and limited their findings to Humans, Adults, and English language results, to identify 10-week mortality data from trials and cohort studies evaluating treatment outcomes of cryptococcal meningitis induction regimens from 1996 onwards in the antiretroviral therapy (ART) era. This search yielded 33 publications. After manually reviewing abstracts and references, 18 studies were included that presented mortality data for HIV-infected adults from resource-limited settings. Rajasingham et al excluded studies that did not report 10-week mortality, and U.S.-based, and European-based CM studies. The systematic review was limited to resource-constrained settings, as a cost-effectiveness analysis would be most pertinent and generalizable to these settings. From these studies, pooled 10-week mortality estimates were calculated for each of the treatment regimens.

Differences in 10-week survival correspond with the known anti-fungal activities of the various induction treatment regimens as quantified by the clearance of *Cryptococcus neoformans* yeast colony forming units (CFU) per mL of cerebrospinal fluid (CSF) per day ($\Delta\log_{10}$ CFU/mL CSF/day) – termed the early fungicidal activity (EFA) [10]. Rhein et al [11] summarizes recent clinical trials that have compared the EFA of various induction treatment regimens.

• ***Summary of available data**** (appraisal of quality, outcome measures, summary of results)

See Table 3 for summary of 10-week mortality outcome measures.
See Table 4 for summary of EFA outcome measures.

Table 3. Cost-effectiveness of cryptococcal treatment outcomes in RLS [2].

Induction Regimen	Induction Duration	10-week Mortality	95% CI	Ref
Fluconazole 800-1200mg	14 days	54.9% (73/133)	46.0-63.5%	[12-15]
Flucytosine + fluconazole 1200mg	14 days	43.5% (20/46)	28.9-58.9%	[15, 16]
Amphotericin + fluconazole 1200mg	5-7 days	26.0% (33/127)	18.6-34.5%	[17-20]
Amphotericin	14 days	34.4% (128/372)	29.6-39.5%	[20-26]
Amphotericin + fluconazole 800mg	14 days	30.0% (61/203)	23.8-36.9%	[25-28]
Amphotericin + flucytosine (5FC)	14 days	26.8% (62/231)	21.2-33.0%	[26-30]

95% CI = 95% confidence interval for the 10-week mortality

Table 4. Trials comparing early fungicidal activity of induction treatment regimens [11]

Cryptococcal Induction Regimen	EFA	± SD	n	Ref
AmB + 5FC	-0.41	0.22	21	[27]
AmB + fluc (800 mg daily)	-0.38	0.18	22	
AmB + fluc (1200 mg daily)	-0.41	0.35	23	
AmB + voriconazole	-0.44	0.20	13	
AmB (short course 5 days) + 5FC	-0.30	0.11	30	[18]
AmB + 5FC	-0.49	NA	30	[30]
AmB + 5FC + INF-γ	-0.64	NA	60	
5FC + fluconazole (1200 mg daily)	-0.28	0.17	21	[15]
Fluconazole (1200 mg daily)	-0.11	0.09	20	
AmB (0.7 mg/kg/day) + 5FC	-0.45	0.16	28	[29]
AmB (1 mg/kg/day) + 5FC	-0.56	0.24	29	
Fluconazole (1200 mg daily)	-0.18	0.11	30	[12]
Fluconazole (800 mg daily)	-0.07	0.17	30	
AmB (1 mg/kg/day)	-0.48	0.28	49	[17]
Fluconazole (400 mg daily)	-0.02	0.05	5	
AmB (0.7 mg/kg/day)	-0.31	0.18	14	[26]
AmB (0.7 mg/kg/day) + 5FC	-0.54	0.19	12	
AmB + fluconazole (400 mg daily)	-0.39	0.15	11	
AmB + 5FC + fluc (400 mg daily)	-0.38	0.13	15	

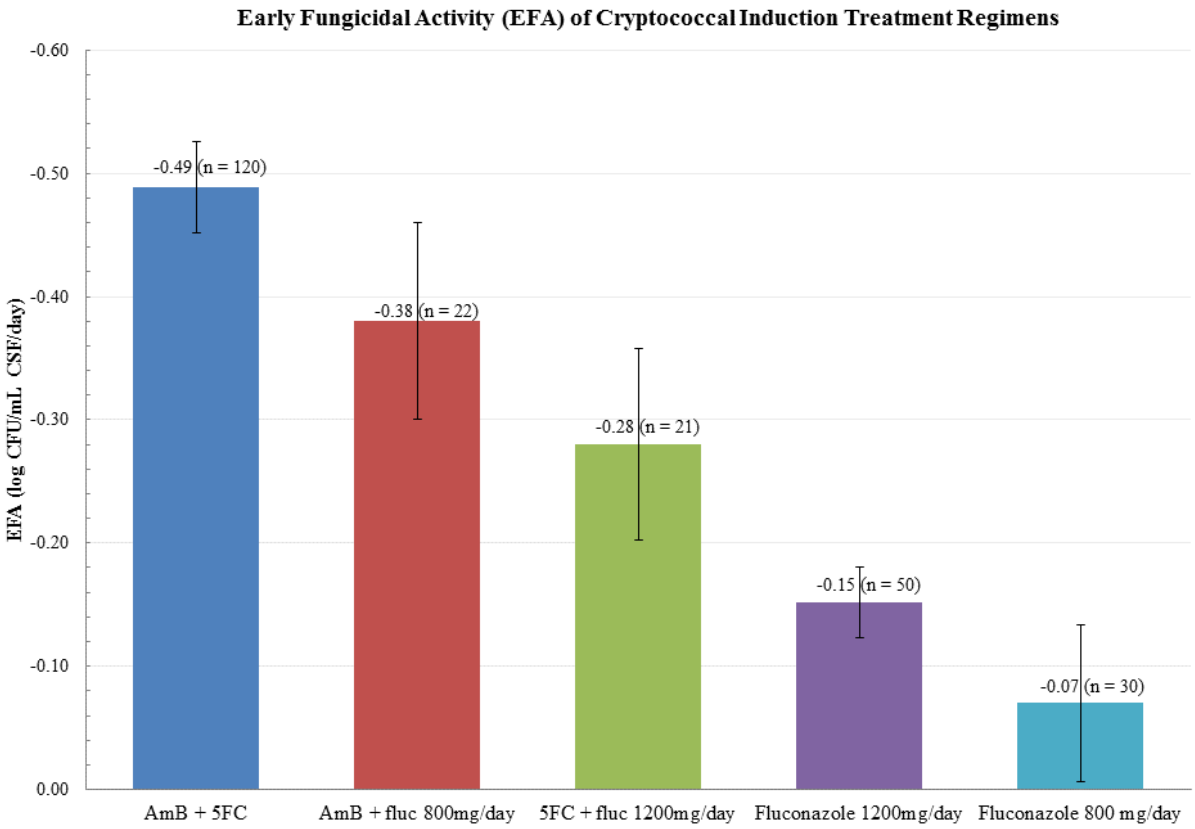
EFA = early fungicidal activity (log CFU/mL CSF/day)
AmB = amphotericin B deoxycholate (0.7 or 1 mg/kg/day or as indicated)
5FC = flucytosine (100mg/kg/day divided 4 times daily)
Fluc = fluconazole (doses indicated)
Voriconazole (300 mg twice daily; 400 mg twice on day 1)
INF-γ = interferon-gamma (100 μg subcutanously, 2 or 6 doses over induction period)

• Summary of available estimates of comparative effectiveness

Amphotericin-based regimens have 25-30% better 10-week survival than fluconazole monotherapy regimens [2]. (Table 3)

Amphotericin-based regimens have superior microbiologic activity with EFA that ranged from -0.38 to -0.49 log CFU/ml CSF/day compared to -0.07 to -0.28 log CFU/ml CSF/day in non-amphotericin based regimens. [11] (Figure 3) For reference, based on a pooled series of Phase II clinical trials, the mean rate of clearance of infection for those who survived at 2 weeks was -0.40 log CFU/ml CSF/day compared to -0.17 log CFU/ml CSF/day in those who died at 2 weeks [10]. At 10 weeks, mean EFA was -0.41 log CFU/ml CSF/day in those who survived compared to -0.27 log CFU/ml CSF/day in those who died [10].

Figure 3. Comparative Early Fungicidal Activity (EFA) of Cryptococcal Induction Treatment Regimens [11]



11. Summary of comparative evidence on safety

• Estimate of total patient exposure to date

Amphotericin B has been used extensively since the 1950s for the treatment of invasive fungal infections including cryptococcosis, aspergillosis, zygomycosis, blastomycosis, coccidiodomycosis, histoplasmosis, and systemic candidiasis.

• Description of adverse effects/reactions

The adverse reactions most commonly observed are (FDA Package Insert):

- *General (body as a whole):* fever (sometimes accompanied by shaking chills usually occurring within 15 to 20 minutes after initiation of treatment); malaise; weight loss.
- *Cardiopulmonary:* hypotension; tachypnea.
- *Gastrointestinal:* anorexia; nausea; vomiting; diarrhea; dyspepsia; cramping epigastric pain.
- *Hematologic:* normochromic, normocytic anemia.
- *Local:* pain at the injection site with or without phlebitis or thrombophlebitis.
- *Musculoskeletal:* generalized pain, including muscle and joint pains.
- *Neurologic:* headache.
- *Renal:* decreased renal function and renal function abnormalities including: azotemia, hypokalemia, hyposthenuria, renal tubular acidosis; and nephrocalcinosis. These usually improve with interruption of therapy. However, some permanent impairment often occurs, especially in those patients receiving large amounts (over 5 g) of

amphotericin B or receiving other nephrotoxic agents. In some patients hydration and sodium repletion prior to amphotericin B administration may reduce the risk of developing nephrotoxicity. Supplemental alkali medication may decrease renal tubular acidosis.

The following adverse reactions have also been reported:

- *General (body as a whole):* flushing
- *Allergic:* anaphylactoid and other allergic reactions; bronchospasm; wheezing.
- *Cardiopulmonary:* cardiac arrest; shock; cardiac failure; pulmonary edema; hypersensitivity pneumonitis; arrhythmias, including ventricular fibrillation; dyspnea; hypertension.
- *Dermatologic:* rash, in particular maculopapular; pruritus.
- *Gastrointestinal:* acute liver failure; hepatitis; jaundice; hemorrghagic gastroenteritis; melena.
- *Hematologic:* agranulocytosis; coagulation defects; thrombocytopenia; leukopenia; eosinophilia; leukocytosis.
- *Neurologic:* convulsions; hearing loss; tinnitus; transient vertigo; visual impairment; diplopia; peripheral neuropathy; encephalopathy; other neurologic symptoms.
- *Renal:* acute renal failure; anuria; oliguria.

Frequency of side effects

In a meta-analysis conducted by Girois et al, infusion related reactions occurred with conventional amphotericin B with the following frequency when data from 48 studies were combined: fever (34%), nausea (19%), rash (3%), and bronchospasm (7%) [31]. Nephrotoxicity occurred in 33% of patients receiving conventional amphotericin B compared to 15% in patients receiving liposomal amphotericin B [31].

Altered Laboratory Findings

- *Serum Electrolytes:* Hypomagnesemia; hypo- and hyperkalemia; hypocalcemia.
- *Liver Function Tests:* Elevations of AST, ALT, GGT, bilirubin, and alkaline phosphatase.
- *Renal Function Tests:* Elevations of BUN and serum creatinine.

• Identification of variation in safety due to health systems and patient factors

Pregnancy

Reproduction studies in animals have revealed no evidence of harm to the fetus due to amphotericin B for injection. Systemic fungal infections have been successfully treated in pregnant women with amphotericin B for injection without obvious effects to the fetus, but the number of cases reported has been small [32]. Because animal reproduction studies are not always predictive of human response, and adequate and well-controlled studies have not been conducted in pregnant women, this drug should be used during pregnancy only if clearly indicated. For cryptococcal meningitis, amphotericin is the drug of choice in pregnant women [8].

• Summary of comparative safety against comparators

Although, Amphotericin B has more frequent serious side effects than fluconazole [31], it is more effective in treating cryptococcal meningitis than other anti-fungal drugs (as described above). The most common adverse reactions (injection

reactions, anemia, hypokalemia, hypomagnesaemia, and renal insufficiency) are often reversible and harm can be mitigated with careful monitoring and treatment. Lipid formulations of amphotericin B have also been shown to be less nephrotoxic.

The 2011 WHO Rapid Advice recommends a core safety package of: intravenous hydration coupled with electrolyte management and monitoring when administering amphotericin. Where monitoring is not possible, WHO recommends 1-week induction therapy. In prior clinical trials severe kidney and electrolyte toxicities did not occur with 1-week of amphotericin [17-19], as the majority of toxicity occurs in the second week of amphotericin.

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

• Range of costs of the proposed medicine

Range of costs for amphotericin B (per 50 mg vial) are summarized in Table 5.

Table 5. Wholesale International Drug Pricing for Amphotericin B (50 mg vial), 2010

International Supplier	Information on supplier	Supplier Prices	Buyer (Country Level)	Buyer Prices
MEDS (Mission for Essential Drugs & Supplies)	Not-for-profit Christian organization. (Coverage: Kenya, Tanzania, Ethiopia, Sudan DRC. HQ Nairobi.)	$ 3.51	South Africa (Department of Health)	$ 4.23
MISSION (Missionpharma)	Supplies generic medicines, medical devices & equipment and medical kits. (Coverage: Africa, India, China. HQ Denmark.)	$ 6.35	Rwanda (Centrale d'achat des Médicaments Essentiels, Consommables et Equipements Médicaux du Rwanda - CAMERWA)	$ 4.65
			Uganda (Uganda National Medical Store -UGANDANMS)	$ 5.00
IDA Foundation	Leading not-for-profit supplier of pharmaceutical products. Supplies 3000 different medicines and medical supplies to over 100 countries worldwide HQ Holland.	$ 7.86	Namibia (Namibia Ministry of Health and Social Services)	$ 6.97
			Barbados Drug Service (BDS)	$ 5.27
			Guatemalan Office of Contracting and Acquisitions	$ 9.75
			Costa Rica Social Security	$ 12.20

Management Sciences for Health International Reference Prices. 2010 data. http://erc.msh.org/dmpguide/resultsdetail.cfm

• Comparative cost-effectiveness presented as range of costs per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality adjusted life year gained).

The cost of cryptococcal care as per WHO guidelines is summarized in Table 6 [2] and is based on the range of 2010 international reference medication costs for

amphotericin (50 mg vial) (median of US$5.27 (range: US$4.23–US$6.97 in Africa), and fluconazole (200-mg tablet), median of US$0.16 (range: US$0.14–US$0.19 in Africa)) [33].

The cost-effectiveness of cryptococcal treatment, comparing the cost of various induction cryptococcal meningitis treatments with expected mean quality adjusted life years (QALY) saved, is summarized in Figure 4.[2]

Table 6. Cost of cryptococcal care (utilizing WHO guidelines) [2]

Induction Regimen	Duration of Induction	Costs					Total Cost of Care
		Medication	3 LPs with Manometers	Hospital Supplies	Lab Costs	Personnel (Uganda)	
Fluconazole 800–1,200 mg	14 d	$8.23 – $12.34	$53.85	$32.63	$36.95	$18.40[a]	$150.06–$154.17
5FC + fluconazole 1,200 mg	14 d	$85.98	$53.85	$32.63	$49.35	$20.74[a]	$242.55
Amphotericin + fluconazole 1,200 mg	7 d	$53.85	$53.85	$54.53	$36.95	$18.40[a]	$217.58
Amphotericin	14 d	$83.02	$53.85	$108.21	$107.35	$41.41	$393.84
Amphotericin + fluconazole 800 mg	14 d	$91.25	$53.85	$108.21	$107.35	$41.41	$402.07
Amphotericin + 5FC	14 d	$156.66	$53.85	$108.21	$107.35	$41.41	$467.48

Figure 4. Cost-effectiveness of comparative cryptococcal meningitis treatment regimens[2]

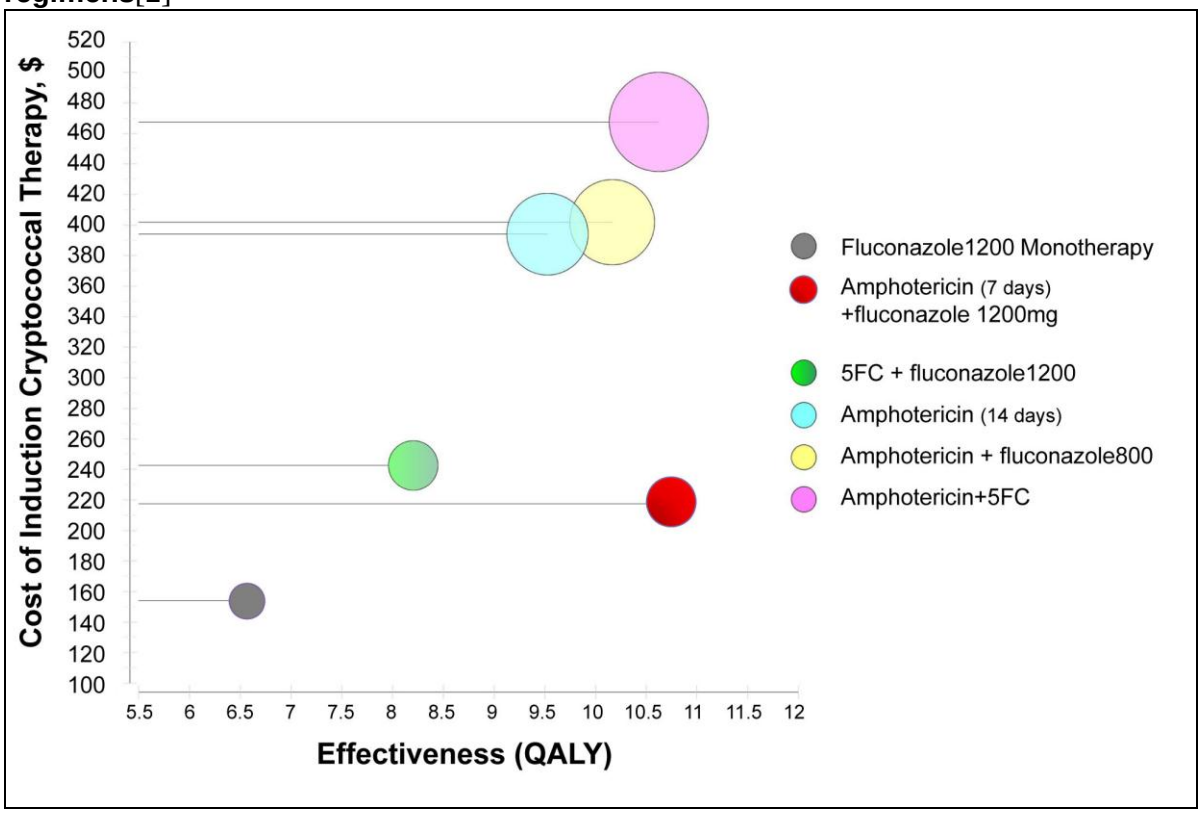


Figure 4 displays the cost of induction therapy for cryptococcal meningitis in resource-limited regions (in US$) versus the effectiveness as measured by QALYs saved per regimen. The radius of the circles represents the standard deviation of the cost estimate. Based on the existing outcome data, the short-course amphotericin (1

mg/day) + fluconazole (1,200 mg/day) regimen has similar effectiveness to but lower costs than traditional 2-week amphotericin-based regimens. This short-course amphotericin + fluconazole regimen has marginally higher cost but significantly greater effectiveness than oral fluconazole-based therapies. Detailed references on model assumptions can be found in Rajasingham et al. [2]

13. Summary of regulatory status of the medicine

Amphotericin is registered in Europe, North and South America, and most Asian countries, including India and China. Registration and availability in Africa is limited.

Table 7. Summary of amphotericin drug registration and availability in Africa

Country	Registered	Available
Cameroon	No	No
Dem. Rep. of Congo	Yes	No
Ethiopia	Yes	No
Guinea	No	No
Kenya	Yes	Yes
South Africa	Yes	Yes
Sudan	Yes	Yes
Swaziland	N/A	Yes
Uganda	No	Special Order

Modified from table at: http://tinyurl.com/857zxdf

14. Availability of pharmacopoeial standards

Current WHO: http://apps.who.int/phint/en/p/docf/
U.S. Full monograph available at:
http://www.drugs.com/monograph/amphotericin-b.html
U.S. brief monograph available at:
https://online.epocrates.com/u/10a91/amphotericin+B+deoxycholate

15. Proposed text for the WHO Model Formulary

amphotericin B deoxycholate	**Powder for injection: 50 mg in vial.**

16. References

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