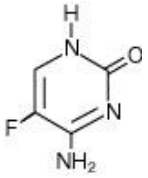
CYTOFLU®
5-Flucytosine Tablets (500 mg)

WARNING

Use with extreme caution in patients with impaired renal function. Close monitoring of hematologic, renal and hepatic status of all patients is essential. These instructions should be thoroughly reviewed before administration of Cytoflu.

DESCRIPTION

Flucytosine is an antifungal agent, is available as 250mg and 500mg tablets for oral administration. Chemically, flucytosine is 5-fluorocytosine, a fluorinated pyrimidine which is related to fluorouracil and floxuridine. It is a white to off-white crystalline powder with a molecular weight of 129.09 and the following structural formula:



CLINICAL PHARMACOLOGY

Flucytosine is rapidly and virtually completely absorbed following oral administration. Flucytosine is not metabolized significantly when given orally to man. Bioavailability estimated by comparing the area under the curve of serum concentrations after oral and intravenous administration showed 78% to 89% absorption of the oral dose. Peak serum concentrations of 30 to 40 µg/mL were reached within 2 hours of administration of a 2g oral dose to normal subjects. Other studies revealed mean serum concentrations of approximately 70 to 80 µg/mL 1 to 2 hours after a dose in patients with normal renal function receiving a 6-week regimen of flucytosine (150 mg/kg/day given in divided doses every 6 hours) in combination with amphotericin B. The half-life in the majority of healthy subjects ranged between 2.4 and 4.8 hours. Flucytosine is excreted via the kidneys by means of glomerular filtration without significant tubular reabsorption. More than 90% of the total radioactivity after oral administration was recovered in the urine as intact drug. Flucytosine is deaminated (probably by gut bacteria) to 5-fluorouracil. The area under the curve (AUC) ratio of 5-fluorouracil to flucytosine is 4%. Approximately 1% of the dose is present in the urine as the α-fluoro-ß-ureido-propionic acid metabolite. A small portion of the dose is excreted in the feces.

The half-life of flucytosine is prolonged in patients with renal insufficiency; the average half-life in nephrectomized or anuric patients was 85 hours (range: 29.9 to 250 hours). A

linear correlation was found between the elimination rate constant of flucytosine and creatinine clearance.

In vitro studies have shown that 2.9% to 4% of flucytosine is protein-bound over the range of therapeutic concentrations found in the blood. Flucytosine readily penetrates the blood-brain barrier, achieving clinically significant concentrations in cerebrospinal fluid.

Pharmacokinetics in Pediatric Patients

Limited data are available regarding the pharmacokinetics of flucytosine administered to neonatal patients being treated for systemic candidiasis. After five days of continuous therapy, median peak levels in infants were 19.6 µg/mL, 27.7 µg/mL, and 83.9 µg/mL at doses of 25 mg/kg (N=3), 50 mg/kg (N=4), and 100 mg/kg (N=3), respectively. Mean time to peak serum levels was of 2.5 ± 1.3 hours, similar to that observed in adult patients. A good deal of interindividual variability was noted, which did not correlate with gestational age. Some patients had serum levels > 100 µg/mL, suggesting a need for drug level monitoring during therapy. In another study, serum concentrations were determined during flucytosine therapy in two patients (total assays performed =10). Median serum flucytosine concentrations at steady state were calculated to be 57 ± 10 µg/mL (doses of 50 to 125 mg/kg/day, normalized to 25 mg/kg per dose for comparison). In three infants receiving flucytosine 25 mg/kg/day (four divided doses), a median flucytosine half-life of 7.4 hours was observed, approximately double that seen in adult patients. The concentration of flucytosine in the cerebrospinal fluid of one infant was 43 µg/mL 3 hours after a 25 mg oral dose, and ranged from 20 to 67 mg/L in another neonate receiving oral doses of 120 to 150 mg/kg/day.

MICROBIOLOGY Mechanism **of Action**

Flucytosine is taken up by fungal organisms via the enzyme cytosine permease. Inside the fungal cell, flucytosine is rapidly converted to fluorouracil by the enzyme cytosine deaminase. Fluorouracil exerts its antifungal activity through the subsequent conversion into several active metabolites, which inhibit protein synthesis by being falsely incorporated into fungal RNA or interfere with the biosynthesis of fungal DNA through the inhibition of the enzyme thymidylate synthetase.

Activity In Vitro

Flucytosine exhibited activity against *Candida* species and *Cryptococcus neoformans*. *In vitro* activity of flucytosine is affected by the test conditions. It is essential to follow the approved standard method guidelines.[1]

Susceptibility Tests

Cryptococcus neoformans:

No interpretive criteria have been established for *Cryptococcus neoformans*[1].

Candida:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of yeasts to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] with standardized inoculum concentrations and standardized concentrations of flucytosine powder. The MIC values should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤4	Susceptible (S)
8-16	Intermediate (I)
≥32	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected. Because of other significant host factors, *in vitro* susceptibility may not correlate with clinical outcomes.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard flucytosine powder should provide the following MIC values:

Acceptable ranges of MICs (µg/mL) for control strains for 48-hour reference broth macrodilution testing:

Microorganism **MIC (µg/mL) [% of data included**]
Candida parapsilosis ATCC 22019 0.12-0.5 [98.6%] *Candida krusei* ATCC 6258 4.0-16 [96.8%]

Acceptable ranges of MICs (µg/mL) for control strains for 24-hour and 48-hour reference broth microdilution testing:

	MIC (µg/mL) ranges for microdilution testing					
	24-hour			48-hour		
Microorganism	Range	Mode	% of data Included	Range	Mode	% of data included

Candida parapsilosis ATCC 22019	0.06-0.25	0.12	99%	0.12-0.5	0.25	98%
Candida krusei ATCC 6258	4.0-16	8.0	98%	8.0-32	16	99%

Drug Resistance

Flucytosine resistance may arise from a mutation of an enzyme necessary for the cellular uptake or metabolism of flucytosine or from an increased synthesis of pyrimidines, which compete with the active metabolites of flucytosine (fluorinated antimetabolites). Resistance to flucytosine has been shown to develop during monotherapy after prolonged exposure to the drug.

Drug Combination

Antifungal synergism between flucytosine and polyene antibiotics, particularly amphotericin B has been reported *in vitro*. Flucytosine is usually administered in combination with amphotericin B due to lack of cross-resistance and reported synergistic activity of both drugs.

Clinical Efficacy (based on published data)

BACKGROUND

Combination antifungal therapy (amphotericin B deoxycholate and flucytosine) is the recommended treatment for cryptococcal meningitis but has not been shown to reduce mortality, as compared with amphotericin B alone. We performed a randomized, controlled trial to determine whether combining flucytosine or high-dose fluconazole with high-dose amphotericin B improved survival at 14 and 70 days.

METHODS

We conducted a randomized, three-group, open-label trial of induction therapy for cryptococcal meningitis in patients with human immunodeficiency virus infection. All patients received amphotericin B at a dose of 1 mg per kilogram of body weight per day; patients in group 1 were treated for 4 weeks, and those in groups 2 and 3 for 2 weeks. Patients in group 2 concurrently received flucytosine at a dose of 100 mg per kilogram per day for 2 weeks, and those in group 3 concurrently received fluconazole at a dose of 400 mg twice daily for 2 weeks.

RESULTS

A total of 299 patients were enrolled. Fewer deaths occurred by days 14 and 70 among patients receiving amphotericin B and flucytosine than among those receiving amphotericin B alone (15 vs. 25 deaths by day 14; hazard ratio, 0.57; 95% confidence

interval [CI], 0.30 to 1.08; unadjusted P=0.08; and 30 vs. 44 deaths by day 70; hazard ratio, 0.61; 95% CI, 0.39 to 0.97; unadjusted P=0.04). Combination therapy with fluconazole had no significant effect on survival, as compared with monotherapy (hazard ratio for death by 14 days, 0.78; 95% CI, 0.44 to 1.41; P=0.42; hazard ratio for death by 70 days, 0.71; 95% CI, 0.45 to 1.11; P=0.13). Amphotericin B plus flucytosine was associated with significantly increased rates of yeast clearance from cerebrospinal fluid (−0.42 log10 colony-forming units [CFU] per milliliter per day vs. −0.31 and −0.32 log10 CFU per milliliter per day in groups 1 and 3, respectively; P<0.001 for both comparisons). Rates of adverse events were similar in all groups, although neutropenia was more frequent in patients receiving a combination therapy.

CONCLUSIONS

Amphotericin B plus flucytosine, as compared with amphotericin B alone, is associated with improved survival among patients with cryptococcal meningitis. A survival benefit of amphotericin B plus fluconazole was not found. (Funded by the Wellcome Trust and the British Infection Society; Controlled-Trials.com number, ISRCTN95123928.)

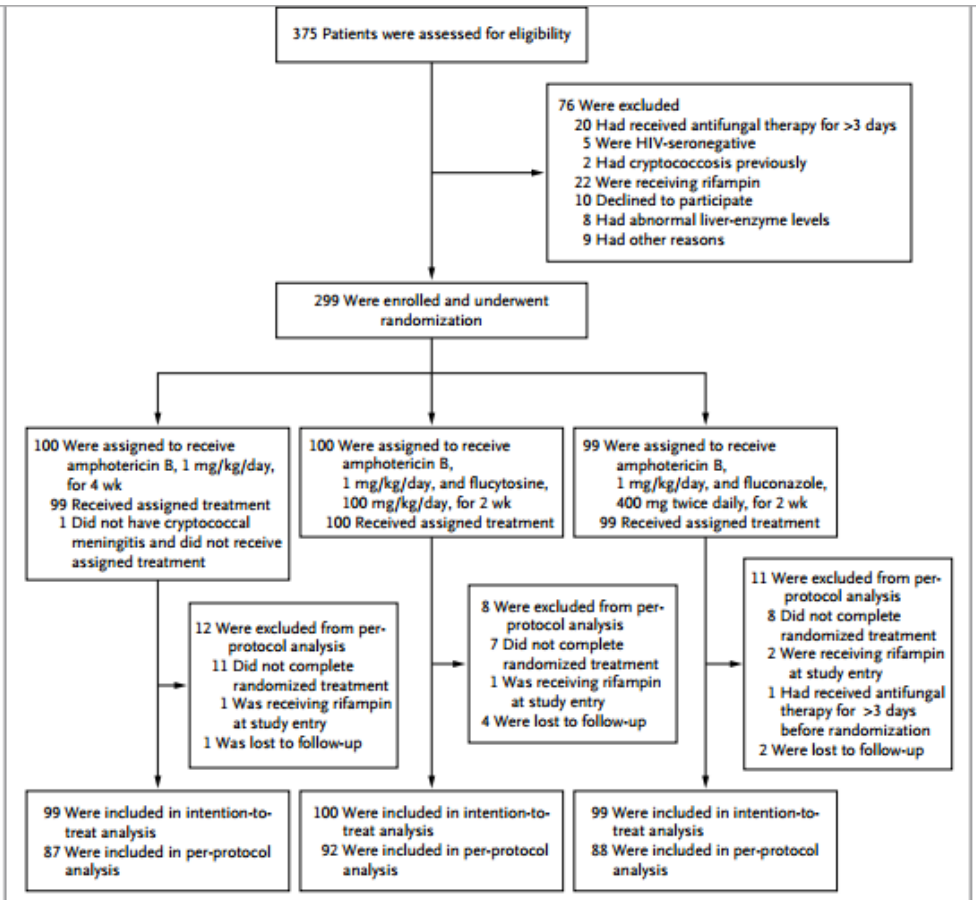


Figure 1. Study Enrollment, Treatment Assignments, and Analysis Populations.

Of 375 patients who underwent assessment, 299 were enrolled in the study. One patient, who underwent randomization but did not have cryptococcal meningitis, did not receive the assigned treatment and was excluded from the intention-to-treat analysis.

Table 1. **Baseline Characteristics of the Study Participants.***

Characteristic	Group 1, Amphotericin B (N=99)	Group 2, Amphotericin B and Flucytosine (N=100)	Group 3, Amphotericin B and Fluconazole (N=99)
Age — yr†			
Median	28	28	27
Interquartile range	25–31	25–33	24–31
Male sex — no. (%)	81 (82)	80 (80)	84 (85)
Intravenous drug use — no./total no. (%)	51/90 (57)	49/94 (52)	53/97 (55)
Duration of symptoms — days‡			
Median	15	14	12
Interquartile range	7–22	8–18	7–20
Headache — no./total no. (%)	95/97 (98)	99/99 (100)	98/99 (99)
Fever — no./total no. (%)	75/97 (77)	75/98 (77)	72/98 (73)
Neck stiffness — no./total no. (%)	66/91 (73)	64/91 (70)	66/95 (69)
Seizure — no./total no. (%)	9/94 (10)	9/98 (9)	2/98 (2)
Glasgow Coma Scale score — no./total no. (%)§			
15	66/97 (68)	67/99 (68)	78/98 (80)
11–14	21/97 (22)	24/99 (24)	15/98 (15)
≤10	10/97 (10)	8/99 (8)	5/98 (5)
Cranial-nerve palsy — no./total no. (%)	27/97 (28)	22/98 (22)	18/98 (18)
Papilledema — no./total no. (%)	18/85 (21)	19/89 (21)	17/93 (18)
CSF opening pressure >18 cm of CSF — no./total no. (%)	56/83 (67)	61/80 (76)	55/81 (68)
CSF white-cell count — cells/ml¶			
Median	33	26	24
Interquartile range	7–76	8–61	7–83
CSF glucose level — mmol/liter‖			
Median	2.21	2.30	2.34
Interquartile range	1.50–3.00	1.70–2.98	1.70–2.99
Plasma glucose level — mmol/liter**			
Median	5.69	5.90	5.43
Interquartile range	4.84–6.50	4.88–6.90	4.80–6.20

Table 1. (Continued.)

Characteristic	Group 1, Amphotericin B (N=99)	Group 2, Amphotericin B and Flucytosine (N=100)	Group 3, Amphotericin B and Fluconazole (N=99)
CSF yeast count — $\log_{10}$ CFU/ml††			
Median	5.91	5.81	5.74
Interquartile range	5.49–6.48	4.74–6.15	4.80–6.34
CD4 count — cells/mm³‡‡			
Median	18	17	14
Interquartile range	8–37	9–28	8–41
Creatinine — μmol/liter§§			
Median	72.0	73.0	70.4
Interquartile range	61.0–93.5	60.0–86.0	61.1–88.5

* There were no significant between-group differences at baseline, with the exception of CSF yeast count (P=0.03 by the Kruskal–Wallis test). For additional details, see Table S1 in the Supplementary Appendix. CFU denotes colony-forming units, and CSF cerebrospinal fluid. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

† Data were missing for 1 patient in group 3.

‡ Data were missing for 14 patients in group 1, for 6 in group 2, and for 8 in group 3.

§ Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating reduced levels of consciousness.

¶ Data were missing for 10 patients in group 1, for 12 in group 2, and for 12 in group 3.

‖ Data were missing for 6 patients in group 2, for 4 in group 2, and for 6 in group 3.

** Data were missing for 8 patients in group 1, for 8 in group 2, and for 6 in group 3.

†† Data were missing for 22 patients in group 1, for 20 in group 2, and for 20 in group 3.

‡‡ Data were missing for 28 patients in group 1, for 26 in group 2, and for 26 in group 3.

§§ Data were missing for 8 patients in group 1, for 3 in group 2, and for 4 in group 3.

Table 2. Primary and Key Secondary Outcomes.*

Outcome	Group 1, Amphotericin B (N=99)	Group 2, Amphotericin B and Flucytosine (N=100)	Group 3, Amphotericin B and Fluconazole (N=99)
Coprimary outcomes			
Death by day 14			
No. of deaths	25	15	20
Probability of survival (95% CI)	0.75 (0.67 to 0.84)	0.85 (0.78 to 0.92)	0.80 (0.73 to 0.88)
Death by day 70‡			
No. of deaths	44	30	33
Probability of survival (95% CI)	0.56 (0.47 to 0.66)	0.69 (0.61 to 0.79)	0.67 (0.58 to 0.77)
Secondary outcomes			
Death by day 70 in the per-protocol population			
No. of deaths/no. of patients included in analysis	37/87	26/92	27/88
Probability of survival (95% CI)	0.58 (0.48 to 0.69)	0.71 (0.63 to 0.81)	0.69 (0.60 to 0.80)
Death by day 182§			
No. of deaths	53	34	45
Probability of survival (95% CI)	0.46 (0.37 to 0.57)	0.65 (0.56 to 0.75)	0.54 (0.45 to 0.65)
Estimated change in CSF fungal count in first 14 days (95% CI) — $\log_{10}$ CFU/ml/day	−0.31 (−0.34 to −0.29)	−0.42 (−0.44 to −0.40)	−0.32 (−0.34 to −0.29)
CSF fungal clearance			
No. of patients with documented clearance	52	74	63
Clearance rate per person-wk of follow-up (95% CI)	0.17 (0.13 to 0.23)	0.39 (0.31 to 0.50)	0.26 (0.20 to 0.34)

* Reported results are for the intention-to-treat population unless otherwise specified and were not adjusted for baseline covariates or multiple comparisons, except for time to CSF fungal clearance, which was adjusted for baseline fungal count. In the coprimary comparisons for death by 14 days and death by 70 days in group 2 versus group 1 and in group 3 versus group 1, conservative Bonferroni multiplicity adjustment would require doubling of the P values (adjustment for multiple primary end points) or would require the P value to be four times as large (adjustment for multiple primary end points and for multiple comparisons of the combination therapies versus a common control group). For disability outcomes, see Table S2 in the Supplementary Appendix.

† Hazard ratios are shown for all outcomes except for the estimated change in CSF fungal count, for which the between-group difference in the estimated change is shown.

‡ When hazard ratios for death by day 70 were adjusted for baseline covariates, the results were as follows: for group 2 versus group 1, the hazard ratio was 0.62 (95% CI, 0.38 to 0.996), P=0.048; for group 3 versus group 1, the hazard ratio was 0.94 (95% CI, 0.58 to 1.51), P=0.80; and for group 2 versus group 3, the hazard ratio was 0.66 (95% CI, 0.39 to 1.10), P=0.11.

§ When hazard ratios for death by day 182 were adjusted for baseline covariates, the results were as follows: for group 2 versus group 1, the hazard ratio was 0.56 (95% CI, 0.36 to 0.87), P=0.01; for group 3 versus group 1, the hazard ratio was 1.01 (95% CI, 0.66 to 1.53), P=0.97; and for group 2 versus group 3, the hazard ratio was 0.55 (95% CI, 0.35 to 0.88), P=0.01.

	Hazard Ratio or Difference in Estimated Change (95% CI)†				
Group 2 vs. Group 1	P Value	Group 3 vs. Group 1	P Value	Group 2 vs. Group 3	P Value
0.57 (0.30 to 1.08)	0.08	0.78 (0.44 to 1.41)	0.42	0.72 (0.37 to 1.41)	0.34
0.61 (0.39 to 0.97)	0.04	0.71 (0.45 to 1.11)	0.13	0.87 (0.53 to 1.42)	0.57
0.60 (0.36 to 0.99)	0.04	0.68 (0.41 to 1.11)	0.12	0.88 (0.52 to 1.51)	0.65
0.56 (0.36 to 0.86)	0.01	0.78 (0.53 to 1.16)	0.23	0.72 (0.46 to 1.12)	0.14
−0.10 (−0.14 to −0.07)	<0.001	0.00 (−0.04 to 0.03)	0.83	−0.10 (−0.14 to −0.07)	<0.001
3.18 (2.17 to 4.66)	<0.001	1.39 (0.94 to 2.07)	0.10	2.29 (1.59 to 3.29)	<0.001

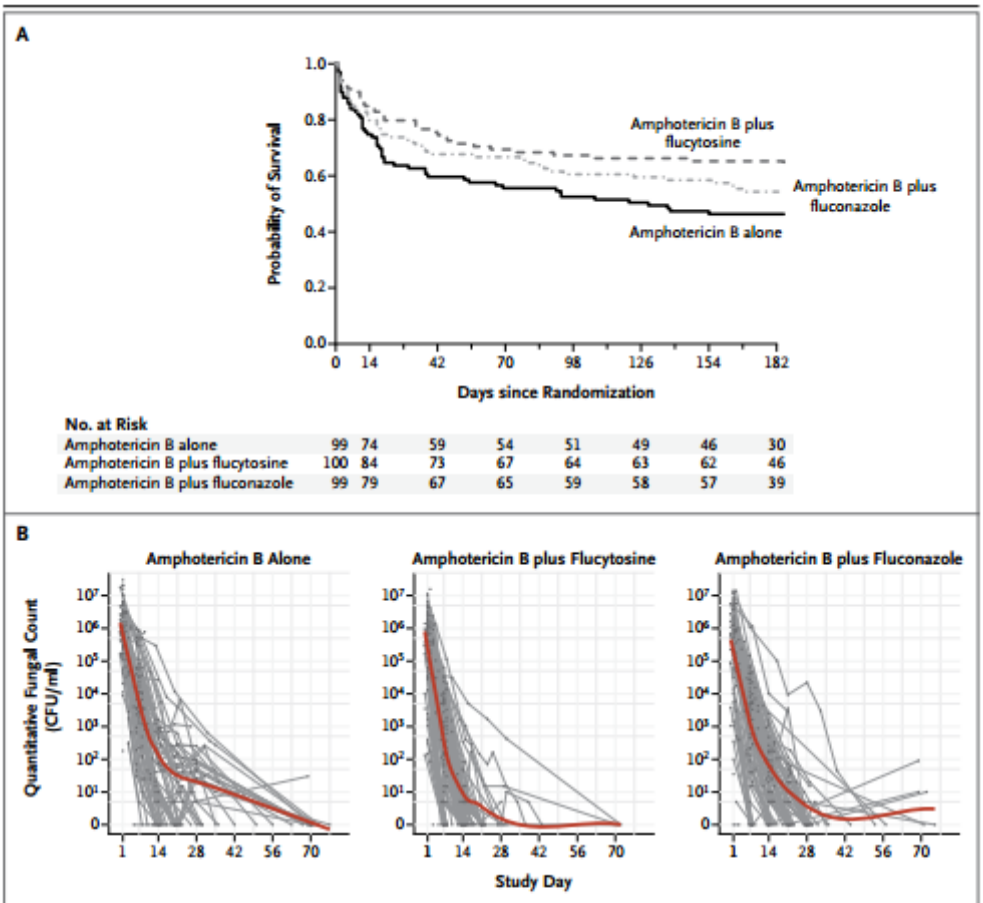


Figure 2. Kaplan–Meier Survival Estimates and Cerebrospinal Fluid (CSF) Fungal Counts, According to Treatment Group.

Panel A shows the Kaplan–Meier survival estimates according to treatment group. For mortality at 70 days, $P=0.04$ for the comparison of amphotericin B plus flucytosine with amphotericin B monotherapy, and $P=0.13$ for the comparison of amphotericin B plus fluconazole with amphotericin B monotherapy. Panel B shows the CSF quantitative fungal counts over time, according to treatment group. Study day 1 corresponds to the day of randomization. All recorded CSF quantitative counts are shown, including those in patients who subsequently died. CSF fungal decline in the first 14 days and time to clearance were significantly faster among patients receiving amphotericin B plus flucytosine than among patients in the other treatment groups ($P<0.001$ for all comparisons). In each graph, gray lines indicate data for individual patients; the red line indicates a loess scatterplot smoother calculated with the use of local regression. CFU denotes colony-forming units.

Table 3. Adverse Events.*

Event	Group 1, Amphotericin B (N=99)	Group 2, Amphotericin B and Flucytosine (N=100)	Group 3, Amphotericin B and Fluconazole (N=99)	P Value†
Any event				
At least one event — no. of patients (%)	82 (83)	85 (85)	85 (86)	0.85
No. of events	338	376	362	
Hypokalemia — no. of patients (%)				
All grades	54 (55)	56 (56)	54 (55)	0.98
Grades 3 and 4	20 (20)	22 (22)	13 (13)	0.24
Anemia — no. of patients (%)				
All grades	62 (63)	63 (63)	57 (58)	0.71
Grades 3 and 4	46 (46)	35 (35)	29 (29)	0.04
Neutropenia — no. of patients (%)				
All grades	19 (19)	34 (34)	32 (32)	0.04
Grades 3 and 4	2 (2)	9 (9)	9 (9)	0.07
Thrombocytopenia — no. of patients (%)				
All grades	8 (8)	15 (15)	11 (11)	0.32
Grades 3 and 4	2 (2)	4 (4)	3 (3)	0.91
Rigor — no. of patients (%)	13 (13)	7 (7)	6 (6)	0.18
Opportunistic infection — no. of patients (%)	32 (32)	32 (32)	28 (28)	0.79
Rash — no. of patients (%)	5 (5)	7 (7)	5 (5)	0.86
New neurologic sign or symptom — no. of patients (%)	11 (11)	12 (12)	10 (10)	0.97
Seizure — no. of patients (%)	2 (2)	0	2 (2)	0.4
Elevated aminotransferase level — no. of patients (%)				
All grades	38 (38)	44 (44)	42 (42)	0.72
Grades 3 and 4	11 (11)	6 (6)	14 (14)	0.14
Hyponatremia — no. of patients (%)				
All grades	28 (28)	33 (33)	33 (33)	0.71
Grades 3 and 4	3 (3)	8 (8)	9 (9)	0.19
Hypercreatinemia — no. of patients (%)				
All grades	34 (34)	41 (41)	46 (46)	0.22
Grades 3 and 4	2 (2)	2 (2)	2 (2)	1.00
Other — no. of patients (%)‡	28 (28)	23 (23)	31 (31)	0.41

INDICATIONS AND USAGE

Flucytosine tablets are indicated only in the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*.

Candida: Septicemia, endocarditis and urinary system infections have been effectively treated with flucytosine. Limited trials in pulmonary infections justify the use of flucytosine.

Cryptococcus: Meningitis and pulmonary infections have been treated effectively. Studies in septicemias and urinary tract infections are limited, but good responses have been reported.

Flucytosine should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of the emergence of resistance to flucytosine (See **MICROBIOLOGY)**.

The following tables have been provided only as a reference to summarize the strength of evidence for the use of Flucytosine in various indications: (Taken from Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America • CID 2010:50 (1 February) • Perfect et al)

Table 1. Strength of Recommendation and Quality of Evidence

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

NOTE. Adapted from the Canadian Task Force on the Periodic Health Examination Health Canada [23]. Reproduced with the permission of the Minister of Public Health Works and Government Services Canada, 2009.

Table 2. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Human Immunodeficiency Virus–Infected Individuals

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)[a]	2 weeks	A-I
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)[a]	2 weeks	B-II
AmBd (0.7–1.0 mg/kg per day) or liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)	4–6 weeks	B-II
Alternatives for induction therapy[b]		
AmBd plus fluconazole	…	B-I
Fluconazole plus flucytosine	…	B-II
Fluconazole	…	B-II
Itraconazole	…	C-II
Consolidation therapy: fluconazole (400 mg per day)	8 weeks	A-I
Maintenance therapy: fluconazole (200 mg per day)[a]	≥1 year[c]	A-I
Alternatives for maintenance therapy[b]		
Itraconazole (400 mg per day)[d]	≥1 year[c]	C-I
AmBd (1 mg/kg per week)[d]	≥1 year[c]	C-I

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate; HAART, highly active antiretroviral therapy.

[a] Begin HAART 2–10 weeks after the start of initial antifungal treatment.

[b] In unique clinical situations in which primary recommendations are not available, consideration of alternative regimens may be made—but not encouraged—as substitutes. See text for dosages.

[c] With successful introduction of HAART, a CD4 cell count ≥100 cells/μL, and low or nondetectable viral load for ≥3 months with minimum of 1 year of antifungal therapy.

[d] Inferior to the primary recommendation.

Table 3. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Transplant Recipients

Regimen	Duration	Evidence
Induction therapy:[a] liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) plus flucytosine (100 mg/kg per day)	2 weeks	B-III
Alternatives for induction therapy		
Liposomal AmB (6 mg/kg per day) or ABLC (5 mg/kg per day)	4–6 weeks	B-III
AmBd (0.7 mg/kg per day)[b]	4–6 weeks	B-III
Consolidation therapy: fluconazole (400–800 mg per day)	8 weeks	B-III
Maintenance therapy: fluconazole (200–400 mg per day)	6 months to 1 year	B-III

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.

[a] Immunosuppressive management may require sequential or step-wise reductions.

[b] Many transplant recipients have been successfully treated with AmBd; however, issues of renal dysfunction with calcineurin inhibitors are important and the effective dose is imprecise.

Table 4. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Non–Human Immunodeficiency Virus–Infected and Nontransplant Patients

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)	≥4 weeks[a,b]	B-II
AmBd (0.7–1.0 mg/kg per day)[c]	≥6 weeks[a,b]	B-II
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) combined with flucytosine, if possible[d]	≥4 weeks[a,b]	B-III
AmBd (0.7 mg/kg per day) plus flucytosine (100 mg/kg per day)[e]	2 weeks	B-II
Consolidation therapy: fluconazole (400–800 mg per day)[f]	8 weeks	B-III
Maintenance therapy: fluconazole (200 mg per day)[b]	6–12 months	B-III

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.

[a] Four weeks are reserved for patients with meningitis who have no neurological complications, who have no significant underlying diseases or immunosuppression, and for whom the cerebrospinal fluid culture performed at the end of 2 weeks of treatment does not yield viable yeasts; during the second 2 weeks, lipid formulations of AmB may be substituted for AmBd.

[b] Fluconazole is given at 200 mg per day to prevent relapse after induction therapy, and consolidation therapy is recommended.

[c] For flucytosine-intolerant patients.

[d] For AmBd-intolerant patients.

[e] For patients who have a low risk of therapeutic failure. Low risk is defined as an early diagnosis by history, no uncontrolled underlying condition or severe immunocompromised state, and an excellent clinical response to initial 2-week antifungal combination course.

[f] A higher dosage of fluconazole (800 mg per day) is recommended if the 2-week induction regimen was used and if there is normal renal function.

Table 5. Antifungal Treatment Recommendations for Nonmeningeal Cryptococcosis

Patient group	Initial antifungal regimen	Duration	Evidence
Immunosuppressed patients and immunocompetent patients with mild-to-moderate pulmonary cryptococcosis	Fluconazole (400 mg per day)	6–12 months	B-III
Immunosuppressed patients[a] and immunocompetent patients with severe pulmonary cryptococcosis	Same as CNS disease	12 months	B-III
Patients with nonmeningeal, nonpulmonary cryptococcosis			
Patients with cryptococcemia	Same as CNS disease	12 months	B-III
Patients for whom CNS disease has been ruled out with no fungemia, with a single site of infection, and with no immunosuppressive risk factors	Fluconazole 400 mg per day	6–12 months	B-III

NOTE. CNS, central nervous system.

[a] Should directly rule out CNS disease with lumbar puncture.

CONTRAINDICATIONS

Flucytosine should not be used in patients with a known hypersensitivity to the drug.

WARNINGS

Flucytosine must be given with extreme caution to patients with impaired renal function. Since flucytosine is excreted primarily by the kidneys, renal impairment may lead to accumulation of the drug. Flucytosine serum concentrations should be monitored to determine the adequacy of renal excretion in such patients. Dosage adjustments should be made in patients with renal insufficiency to prevent progressive accumulation of active drug.

Flucytosine must be given with extreme caution to patients with bone marrow depression. Patients may be more prone to depression of bone marrow function if they: 1) have a hematologic disease, 2) are being treated with radiation or drugs which depress bone marrow, or 3) have a history of treatment with such drugs or radiation. Bone marrow toxicity can be irreversible and may lead to death in immunosuppressed patients. Frequent monitoring of hepatic function and of the hematopoietic system is indicated during therapy.

PRECAUTIONS

Before therapy with Flucytosine is instituted, electrolytes (because of hypokalemia) and the hematologic and renal status of the patient should be determined (see **WARNINGS**). Close monitoring of the patient during therapy is essential.

Laboratory Tests

Since renal impairment can cause progressive accumulation of the drug, blood concentrations and kidney function should be monitored during therapy. Hematologic status (leucocyte and thrombocyte count) and liver function (alkaline phosphatase, SGOT and SGPT) should be determined at frequent intervals during treatment as indicated.

Drug Interactions
Cytosine arabinoside, a cytostatic agent, has been reported to inactivate the antifungal activity of flucytosine by competitive inhibition. Drugs which impair glomerular filtration may prolong the biological half-life of flucytosine.

Drug/Laboratory Test Interactions
Measurement of serum creatinine levels should be determined by the Jaffé reaction, since Flucytosine does not interfere with the determination of creatinine values by this method. Most automated equipment for measurement of creatinine makes use of the Jaffé reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Flucytosine has not undergone adequate animal testing to evaluate carcinogenic potential. The mutagenic potential of flucytosine was evaluated in Ames-type studies with five different mutants of *S. typhimurium* and no mutagenicity was detected in the presence or absence of activating enzymes. Flucytosine was nonmutagenic in three different repair assay systems (i.e., rec, uvr and pol).

There have been no adequate trials in animals on the effects of flucytosine on fertility or reproductive performance. The fertility and reproductive performance of the offspring (F_1 generation) of mice treated with 100 mg/kg/day (345 mg/M^2/day or 0.059 times the human dose), 200 mg/kg/day (690 mg/M^2/day or 0.118 times the human dose) or 400 mg/kg/day (1380 mg/M^2/day or 0.236 times the human dose) of flucytosine on days 7 to 13 of gestation was studied; the *in utero* treatment had no adverse effect on the fertility or reproductive performance of the offspring.

Pregnancy: Teratogenic Effects. Pregnancy Category C
Flucytosine was shown to be teratogenic (vertebral fusions) in the rat at doses of 40 mg/kg/day (298 mg/M^2/day or 0.051 times the human dose) administered on days 7 to 13 of gestation. At higher doses (700 mg/kg/day; 5208 mg/M^2/day or 0.89 times the human dose administered on days 9 to 12 of gestation), cleft lip and palate and micrognathia were reported. Flucytosine was not teratogenic in rabbits up to a dose of 100 mg/kg/day (1423 mg/M^2/day or 0.243 times the human dose) administered on days 6 to 18 of gestation. In mice, 400 mg/kg/day of flucytosine (1380 mg/M^2/day or 0.236 times the human dose) administered on days 7 to 13 of gestation was associated with a low incidence of cleft palate that was not statistically significant. There are no adequate and well-controlled studies in pregnant women. Flucytosine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Flucytosine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The efficacy and safety of flucytosine have not been systematically studied in pediatric patients. A small number of neonates have been treated with 25 to 200 mg/kg/day of flucytosine, with and without the addition of amphotericin B, for systemic candidiasis. No unexpected adverse reactions were reported in these patients. It should be noted, however, that hypokalemia and acidemia were reported in one patient who received flucytosine in combination with amphotericin B, and anemia was observed in a second patient who received flucytosine alone. Transient thrombocytopenia was noted in two additional patients, one of whom also received amphotericin B.

ADVERSE REACTIONS

The adverse reactions which have occurred during treatment with flucytosine are grouped according to organ system affected.

Cardiovascular: Cardiac arrest, myocardial toxicity, ventricular dysfunction.

Respiratory: Respiratory arrest, chest pain, dyspnea.

Dermatologic: Rash, pruritus, urticaria, photosensitivity.

Gastrointestinal: Nausea, emesis, abdominal pain, diarrhea, anorexia, dry mouth, duodenal ulcer, gastrointestinal hemorrhage, acute hepatic injury with possible fatal outcome in debilitated patients, hepatic dysfunction, jaundice, ulcerative colitis, bilirubin elevation, increased hepatic enzymes.

Genitourinary: Azotemia, creatinine and BUN elevation, crystalluria, renal failure.

Hematologic: Anemia, agranulocytosis, aplastic anemia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia

Neurologic: Ataxia, hearing loss, headache, paresthesia, parkinsonism, peripheral neuropathy, pyrexia, vertigo, sedation, convulsions.

Psychiatric: Confusion, hallucinations, psychosis.

Miscellaneous: Fatigue, hypoglycemia, hypokalemia, weakness, allergic reactions, Lyell's syndrome.

OVERDOSAGE

There is no experience with intentional overdosage. It is reasonable to expect that overdosage may produce pronounced manifestations of the known clinical adverse reactions. Prolonged serum concentrations in excess of 100 µg/mL may be associated with an increased incidence of toxicity, especially gastrointestinal (diarrhea, nausea, vomiting), hematologic (leukopenia, thrombocytopenia) and hepatic (hepatitis).

In the management of overdosage, prompt gastric lavage or the use of an emetic is recommended. Adequate fluid intake should be maintained, by the intravenous route if necessary, since flucytosine is excreted unchanged via the renal tract. The hematologic parameters should be monitored frequently; liver and kidney function should be carefully monitored. Should any abnormalities appear in any of these parameters, appropriate therapeutic measures should be instituted.

Since hemodialysis has been shown to rapidly reduce serum concentrations in anuric patients, this method may be considered in the management of overdosage.

DOSAGE AND ADMINISTRATION

The usual dosage of Flucytosine is 50 to 150 mg/kg/day administered in divided doses at 6hour intervals. Nausea or vomiting may be reduced or avoided if the capsules are given a few at a time over a 15-minute period. If the BUN or the serum creatinine is elevated, or if there are other signs of renal impairment, the initial dose should be at the lower level (see **WARNINGS**).

Flucytosine should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of the emergence of resistance to flucytosine (See **MICROBIOLOGY).**

HOW SUPPLIED

Tablets, 500 mg, imprinted CYTOFLU® 500, bottles of 100.
Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F).

REFERENCES

1: Clinical and Laboratory Standards Institute. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard-Second Edition. NCCLS Document M27-A2, 2002 Volume 22, No 15, NCCLS, Wayne, PA, August 2002.

2: Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America; Perfect et al CID 2010:50

3: Combination Antifungal Therapy for Cryptococcal Meningitis; Day et al; N Engl J Med 2013;368:1291-302. DOI: 10.1056/NEJMoa1110404

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