

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-506

APPROVED LABELING



Fujisawa

Mycamine™

(micafungin sodium) For Injection

INTRAVENOUS INFUSION (not for IV bolus injection)

DESCRIPTION:

MYCAMINE is a sterile, lyophilized product for intravenous (IV) infusion that contains micafungin sodium. Micafungin sodium is a semisynthetic lipopeptide (echinocandin) synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin inhibits the synthesis of 1, 3-β-D-glucan, an integral component of the fungal cell wall.

Each single-use vial contains 50 mg micafungin sodium, 200 mg lactose, with citric acid and/or sodium hydroxide (used for pH adjustment). MYCAMINE must be diluted with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP (see **DOSAGE AND ADMINISTRATION**). Following reconstitution with 0.9% Sodium Chloride Injection, USP, the resulting pH of the solution is between 5.0-7.0.

23 Micafungin sodium is chemically designated as:

24 Pneumocandin A0, 1-[(4*R*,5*R*)-4,5-dihydroxy-*N*²-[4-[5-[4-(pentyloxy)phenyl]-3-
25 isoxazolyl]benzoyl]-L-ornithine]-4-[(4*S*)-4-hydroxy-4-[4-hydroxy-3-
26 (sulfooxy)phenyl]-L-threonine]-, monosodium salt.

27

28 The chemical structure of micafungin sodium is:

29

30

31

32

33

34

35

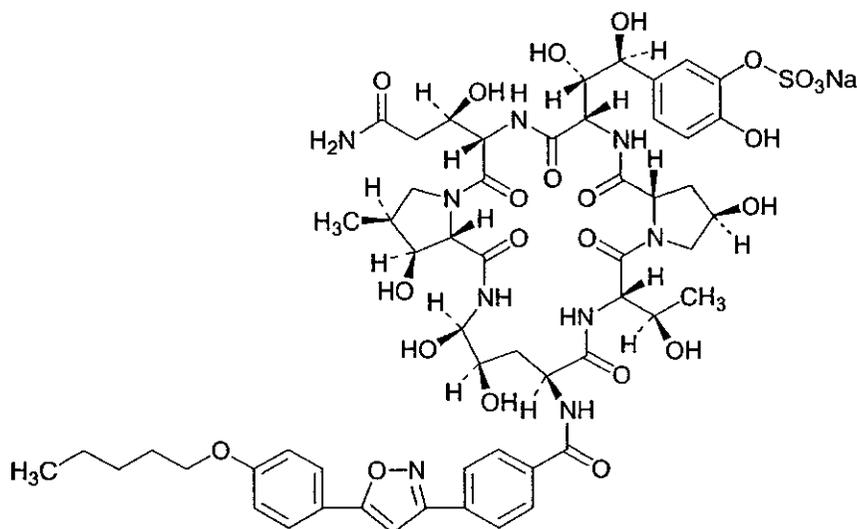
36

37

38

39

40



41 The empirical/molecular formula is C₅₆H₇₀N₉NaO₂₃S and the formula weight is

42 1292.26.

43

44 Micafungin sodium is a light-sensitive, hygroscopic white powder that is freely
45 soluble in water, isotonic sodium chloride solution, *N,N*-dimethylformamide and
46 dimethylsulfoxide, slightly soluble in methyl alcohol, and practically insoluble in
47 acetonitrile, ethyl alcohol (95%), acetone, diethyl ether and *n*-hexane.

48

49 **CLINICAL PHARMACOLOGY:**

50 **Pharmacokinetics**

51 The pharmacokinetics of micafungin were determined in healthy subjects,
52 hematopoietic stem cell transplant recipients, and patients with esophageal
53 candidiasis up to a maximum daily dose of 8 mg/kg body weight.

54 The relationship of area under the concentration-time curve (AUC) to micafungin
 55 dose was linear over the daily dose range of 50 mg to 150 mg and 3 mg/kg to 8
 56 mg/kg body weight.

57

58 Steady-state pharmacokinetic parameters in relevant patient populations after
 59 repeated daily administration are presented in the table below.

60

61 **Table 1: Pharmacokinetic Parameters of Micafungin in Adult Patients**

Population	N	Dose (mg)	Pharmacokinetic Parameters (Mean ± Standard Deviation)			
			C _{max} (mcg/mL)	AUC ₀₋₂₄ (mcg-h/mL)	t _{1/2} (h)	Cl (mL/min/kg)
HIV-Positive Patients with EC [Day 14 or 21]	20	50	5.1±1.0	54±13	15.6±2.8	0.300±0.063
	20	100	10.1±2.6	115±25	16.9±4.4	0.301±0.086
	14	150	16.4±6.5	167±40	15.2±2.2	0.297±0.081
HSCT Recipients [Day 7]	8	<i>per kg</i> 3	21.1±2.84	234±34	14.0±1.4	0.214±0.031
	10	4	29.2±6.2	339±72	14.2±3.2	0.204±0.036
	8	6	38.4±6.9	479±157	14.9±2.6	0.224±0.064
	8	8	60.8±26.9	663±212	17.2±2.3	0.223±0.081

62 HIV=human immunodeficiency virus; EC = esophageal candidiasis; HSCT = hematopoietic stem
 63 cell transplant

64

65 **Distribution**

66 The mean ± standard deviation volume of distribution of micafungin at terminal
 67 phase was 0.39 ± 0.11 L/kg body weight when determined in adult patients with
 68 esophageal candidiasis at the dose range of 50 mg to 150 mg.

69

70 Micafungin is highly (>99%) protein bound *in vitro*, independent of plasma
 71 concentrations over the range of 10 to 100 mcg/mL. The primary binding protein
 72 is albumin; however, micafungin, at therapeutically relevant concentrations, does
 73 not competitively displace bilirubin binding to albumin. Micafungin also binds to
 74 a lesser extent to α₁-acid-glycoprotein.

75

76 **Metabolism**

77 Micafungin is metabolized to M-1 (catechol form) by arylsulfatase, with further
78 metabolism to M-2 (methoxy form) by catechol-*O*-methyltransferase. M-5 is
79 formed by hydroxylation at the side chain (ω -1 position) of micafungin catalyzed
80 by cytochrome P450 (CYP) isozymes. Even though micafungin is a substrate for
81 and a weak inhibitor of CYP3A *in vitro*, hydroxylation by CYP3A is not a major
82 pathway for micafungin metabolism *in vivo*. Micafungin is neither a P-
83 glycoprotein substrate nor inhibitor *in vitro*.

84

85 In four healthy volunteer studies, the ratio of metabolite to parent exposure
86 (AUC) at a dose of 150 mg/day was 6% for M-1, 1% for M-2, and 6% for M-5.
87 In patients with esophageal candidiasis, the ratio of metabolite to parent exposure
88 (AUC) at a dose of 150 mg/day was 11% for M-1, 2% for M-2, and 12% for M-5.

89

90 **Excretion**

91 The excretion of radioactivity following a single intravenous dose of ¹⁴C-
92 micafungin sodium for injection (25 mg) was evaluated in healthy volunteers. At
93 28 days after administration, mean urinary and fecal recovery of total
94 radioactivity accounted for 82.5% (76.4 to 87.9%) of the administered dose.
95 Fecal excretion is the major route of elimination (total radioactivity at 28 days
96 was 71.0% of the administered dose).

97

98 **Special Populations**

99 MYCAMINE disposition has been studied in a variety of populations as described
100 below.

101

102 *Race and Gender*

103 No dose adjustment of MYCAMINE is required based on gender or race. After
104 14 daily doses of 150 mg to healthy subjects, micafungin AUC in women was

105 greater by approximately 23% compared with men, due to smaller body weight.
106 No notable differences among white, black, and Hispanic subjects were seen. The
107 micafungin AUC was greater by 26% in Japanese subjects compared to blacks,
108 due to smaller body weight.

109

110 *Renal Insufficiency*

111 MYCAMINE does not require dose adjustment in patients with renal impairment.
112 A single 1-hour infusion of 100 mg MYCAMINE was administered to 9 subjects
113 with severe renal dysfunction (creatinine clearance <30 mL/min) and to 9 age-,
114 gender-, and weight-matched subjects with normal renal function (creatinine
115 clearance >80 mL/min). The maximum concentration (C_{max}) and AUC were not
116 significantly altered by severe renal impairment.

117

118 Since micafungin is highly protein bound, it is not dialyzable. Supplementary
119 dosing should not be required following hemodialysis.

120

121 *Hepatic Insufficiency*

122 A single 1-hour infusion of 100 mg MYCAMINE was administered to 8 subjects
123 with moderate hepatic dysfunction (Child-Pugh score 7-9) and 8 age-, gender-,
124 and weight-matched subjects with normal hepatic function. The C_{max} and AUC
125 values of micafungin were lower by approximately 22% in subjects with
126 moderate hepatic insufficiency. This difference in micafungin exposure does not
127 require dose adjustment of MYCAMINE in patients with moderate hepatic
128 impairment. The pharmacokinetics of MYCAMINE have not been studied in
129 patients with severe hepatic insufficiency.

130

131 *Geriatric*

132 The exposure and disposition of a 50 mg MYCAMINE dose administered as a
133 single 1-hour infusion to 10 healthy subjects aged 66-78 years were not

134 significantly different from those in 10 healthy subjects aged 20-24 years. No
135 dose adjustment is necessary for the elderly.

136

137 **MICROBIOLOGY:**

138 **Mechanism of Action**

139 Micafungin, the active ingredient in MYCAMINE, inhibits the synthesis of 1,3- β -
140 D-glucan, an essential component of fungal cell walls, which is not present in
141 mammalian cells.

142

143 **Activity *In Vitro***

144 Micafungin exhibited *in-vitro* activity against *C. albicans*, *C. glabrata*, *C. krusei*,
145 *C. parapsilosis*, and *C. tropicalis*. Standardized susceptibility testing methods for
146 1,3- β -D-glucan synthesis inhibitors have not been established, and the results of
147 susceptibility studies do not correlate with clinical outcome.

148

149 **Activity *In Vivo***

150 Micafungin sodium has shown activity in both mucosal and disseminated murine
151 models of candidiasis. Micafungin sodium, administered to immunosuppressed
152 mice in models of disseminated candidiasis prolonged survival and/or decreased
153 the mycological burden.

154

155 **Drug Resistance**

156 The potential for development of drug resistance is not known.

157

158 **INDICATIONS AND USAGE:**

159 MYCAMINE is indicated for:

160

- 161 • Treatment of patients with esophageal candidiasis (see **CLINICAL**
162 **STUDIES, MICROBIOLOGY**)
- 163 • Prophylaxis of *Candida* infections in patients undergoing hematopoietic
164 stem cell transplantation (see **CLINICAL STUDIES,**
165 **MICROBIOLOGY**).

166

167 **NOTE:** The efficacy of MYCAMINE against infections caused by fungi other
168 than *Candida* has not been established.

169

170 **CONTRAINDICATIONS:**

171 MYCAMINE is contraindicated in patients with hypersensitivity to any
172 component of this product.

173

174 **WARNINGS:**

175 Isolated cases of serious hypersensitivity (anaphylaxis and anaphylactoid)
176 reactions (including shock) have been reported in patients receiving
177 MYCAMINE. If these reactions occur, MYCAMINE infusion should be
178 discontinued and appropriate treatment administered.

179

180 **PRECAUTIONS:**

181 **Hepatic Effects**

182 Laboratory abnormalities in liver function tests have been seen in healthy
183 volunteers and patients treated with MYCAMINE. In some patients with serious
184 underlying conditions who were receiving MYCAMINE along with multiple
185 concomitant medications, clinical hepatic abnormalities have occurred, and
186 isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic
187 failure have been reported. Patients who develop abnormal liver function tests
188 during MYCAMINE therapy should be monitored for evidence of worsening

189 hepatic function and evaluated for the risk/benefit of continuing MYCAMINE
190 therapy.

191

192 **Renal Effects**

193 Elevations in BUN and creatinine, and isolated cases of significant renal
194 dysfunction or acute renal failure have been reported in patients who received
195 MYCAMINE. In controlled trials, the incidence of drug-related renal adverse
196 events was 0.4% for MYCAMINE treated patients and 0.5% for fluconazole
197 treated patients. Patients who develop abnormal renal function tests during
198 MYCAMINE therapy should be monitored for evidence of worsening renal
199 function.

200

201 **Hematological Effects**

202 Acute intravascular hemolysis and hemoglobinuria was seen in a healthy
203 volunteer during infusion of MYCAMINE (200 mg) and oral prednisolone (20
204 mg). This event was transient, and the subject did not develop significant anemia.
205 Isolated cases of significant hemolysis and hemolytic anemia have also been
206 reported in patients treated with MYCAMINE. Patients who develop clinical or
207 laboratory evidence of hemolysis or hemolytic anemia during MYCAMINE
208 therapy should be monitored closely for evidence of worsening of these
209 conditions and evaluated for the risk/benefit of continuing MYCAMINE therapy.

210

211 **Drug Interactions**

212 A total of 11 clinical drug-drug interaction studies were conducted in healthy
213 volunteers to evaluate the potential for interaction between MYCAMINE and
214 mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus,
215 nifedipine, fluconazole, ritonavir, and rifampin. In these studies, no interaction
216 that altered the pharmacokinetics of micafungin was observed.

217

218 There was no effect of a single dose or multiple doses of MYCAMINE on
219 mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole
220 pharmacokinetics.

221

222 Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of
223 steady-state MYCAMINE compared with sirolimus alone. Nifedipine AUC and
224 C_{max} were increased by 18% and 42%, respectively, in the presence of steady-
225 state MYCAMINE compared with nifedipine alone. Patients receiving sirolimus
226 or nifedipine in combination with MYCAMINE should be monitored for
227 sirolimus or nifedipine toxicity and sirolimus or nifedipine dosage should be
228 reduced if necessary.

229

230 Micafungin is not an inhibitor of P-glycoprotein and, therefore, would not be
231 expected to alter P-glycoprotein-mediated drug transport activity.

232

233 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

234 No life-time studies in animals were performed to evaluate the carcinogenic
235 potential of MYCAMINE. Micafungin sodium was not mutagenic or clastogenic
236 when evaluated in a standard battery of *in-vitro* and *in-vivo* tests (i.e., bacterial
237 reversion - *S. typhimurium*, *E. coli*; chromosomal aberration; intravenous mouse
238 micronucleus).

239

240 Male rats treated intravenously with micafungin sodium for 9 weeks showed
241 vacuolation of the epididymal ductal epithelial cells at or above 10 mg/kg (about
242 0.6 times the recommended clinical dose for esophageal candidiasis, based on
243 body surface area comparisons). Higher doses (about twice the recommended
244 clinical dose, based on body surface area comparisons) resulted in higher
245 epididymis weights and reduced numbers of sperm cells. In a 39-week
246 intravenous study in dogs, seminiferous tubular atrophy and decreased sperm in
247 the epididymis were observed at 10 and 32 mg/kg, doses equal to about 2 and 7

248 times the recommended clinical dose, based on body surface area comparisons.
249 There was no impairment of fertility in animal studies with micafungin sodium.
250

251 **Pregnancy Category C**

252 Micafungin sodium administration to pregnant rabbits (intravenous dosing on
253 days 6 to 18 of gestation) resulted in visceral abnormalities and abortion at 32
254 mg/kg, a dose equivalent to about four times the recommended dose based on
255 body surface area comparisons. Visceral abnormalities included abnormal
256 lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian
257 artery, and dilatation of the ureter.

258

259 However, adequate, well-controlled studies were not conducted in pregnant
260 women. Animal studies are not always predictive of human response; therefore,
261 MYCAMINE should be used during pregnancy only if clearly needed.

262

263 **Nursing Mothers**

264 Micafungin was found in the milk of lactating, drug-treated rats. It is not known
265 whether micafungin is excreted in human milk. Caution should be exercised
266 when MYCAMINE is administered to a nursing woman.

267

268 **Pediatric Use**

269 The safety and efficacy of MYCAMINE in pediatric patients has not been
270 established in clinical studies.

271

272 **Geriatric Use**

273 A total of 186 subjects in clinical studies of MYCAMINE were 65 years of age
274 and older, and 41 subjects were 75 years of age and older. No overall differences
275 in safety or effectiveness were observed between these subjects and younger

276 subjects. Other reported clinical experience has not identified differences in
277 responses between the elderly and younger patients, but greater sensitivity of
278 some older individuals cannot be ruled out.

279

280 **ADVERSE REACTIONS:**

281 **General**

282 Possible histamine-mediated symptoms have been reported with MYCAMINE,
283 including rash, pruritus, facial swelling, and vasodilatation.

284

285 Injection site reactions, including phlebitis and thrombophlebitis have been
286 reported, at MYCAMINE doses of 50-150 mg/day. These events tended to occur
287 more often in patients receiving MYCAMINE via peripheral intravenous
288 administration.

289

290 **Clinical Adverse Experiences**

291 Because clinical trials are conducted under widely varying conditions, adverse
292 reaction rates observed in clinical trials of MYCAMINE cannot be directly
293 compared to rates in clinical trials of another drug and may not reflect the rates
294 observed in practice. The adverse reaction information from clinical trials does
295 provide a basis for identifying adverse events that appear to be related to drug use
296 and for approximating rates.

297

298 **Esophageal Candidiasis**

299 In a phase 3, randomized, double-blind study for treatment of esophageal
300 candidiasis, a total of 202/260 (77.7%) patients who received MYCAMINE 150
301 mg/day and 186/258 (72.1%) patients who received intravenous fluconazole 200
302 mg/day experienced an adverse event. Adverse events considered to be drug-
303 related occurred in 72 (27.7%) and 55 (21.3%) patients in the MYCAMINE and

304 fluconazole treatment groups, respectively. Drug-related adverse events resulting
305 in discontinuation were reported in 6 (2.3%) MYCAMINE treated patients; and in
306 2 (0.8%) fluconazole treated patients. Rash and delirium were the most common
307 drug-related adverse events resulting in MYCAMINE discontinuation. Drug-
308 related adverse experiences occurring in $\geq 0.5\%$ of the patients in either treatment
309 group are shown in Table 2.

310
311

Table 2: Common Drug-Related * Adverse Events Among Patients with Esophageal Candidiasis

Adverse Events ⁽¹⁾ (MedDRA System Organ Class and Preferred Term)	MYCAMINE 150 mg/day n (%)	Fluconazole 200 mg/day n (%)
Number of Patients	260	258
Blood and Lymphatic System Disorders		
Leukopenia	7 (2.7)	2 (0.8)
Neutropenia	3 (1.2)	1 (0.4)
Thrombocytopenia	3 (1.2)	4 (1.6)
Anemia	3 (1.2)	4 (1.6)
Lymphopenia	2 (0.8)	1 (0.4)
Eosinophilia	0	2 (0.8)
Gastrointestinal Disorders		
Nausea	6 (2.3)	7 (2.7)
Abdominal Pain	5 (1.9)	4 (1.6)
Vomiting	3 (1.2)	4 (1.6)
General Disorders and Administration Site Conditions		
Rigors	6 (2.3)	0
Pyrexia	5 (1.9)	1 (0.4)
Infusion Site Inflammation	4 (1.5)	3 (1.2)
Laboratory Tests		
Blood Alkaline Phosphatase Increased	4 (1.5)	4 (1.6)
Aspartate Aminotransferase Increased	2 (0.8)	4 (1.6)
Blood Lactate Dehydrogenase Increased	2 (0.8)	3 (1.2)
Transaminases Increased	2 (0.8)	1 (0.4)
Alanine Aminotransferase Increased	1 (0.4)	5 (1.9)
Metabolism and Nutrition Disorders		
Hypomagnesemia	0	3 (1.2)
Nervous System Disorders		
Headache	7 (2.7)	3 (1.2)
Dizziness	1 (0.4)	2 (0.8)
Somnolence	1 (0.4)	7 (2.7)
Psychiatric Disorders		
Delirium	2 (0.8)	2 (0.8)
Skin and Subcutaneous Tissue Disorders		
Rash	8 (3.1)	5 (1.9)
Pruritus	3 (1.2)	3 (1.2)
Vascular Disorders		
Phlebitis	11 (4.2)	6 (2.3)

312
313
314
315
316
317

Patient base: all randomized patients who received at least 1 dose of trial drug

Common: $\geq 0.5\%$ in either treatment arm.

*Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.

⁽¹⁾ Within a system organ class patients may experience more than 1 adverse event.

318 **Prophylaxis of *Candida* Infections in Hematopoietic Stem Cell**
319 **Transplant Recipients**

320 A double-blind, phase 3 study was conducted in a total of 882 patients scheduled
321 to undergo an autologous or allogeneic hematopoietic stem cell transplant. The
322 median duration of treatment was 18 days (range 1 to 51 days) in both treatment
323 arms.

324

325 All patients who received MYCAMINE (425) and all patients who received
326 fluconazole (457) experienced at least one adverse event during the study. Drug-
327 related adverse events occurred in 64/425 (15.1%) and 77/457 (16.8%) patients in
328 the MYCAMINE and fluconazole treatment groups, respectively. Drug-related
329 adverse events resulting in MYCAMINE discontinuation were reported in 11
330 (2.6%) patients; while those resulting in fluconazole discontinuation were
331 reported in 16 (3.5%). Drug-related adverse experiences occurring in $\geq 0.5\%$ of
332 the patients in either treatment group are shown in Table 3.

333

334

335

Table 3: Common Adverse Events Related* to Study Drug in Clinical Study of Prophylaxis of *Candida* Infection in Hematopoietic Stem Cell Transplant Recipients

Adverse Events ⁽¹⁾ (MedDRA System Organ Class and Preferred Term)	MYCAMINE 50 mg/day n (%)	Fluconazole 400 mg/day n (%)
Number of Patients	425	457
Blood and Lymphatic System Disorders		
Neutropenia	5 (1.2)	4 (0.9)
Anemia	4 (0.9)	3 (0.7)
Febrile neutropenia	4 (0.9)	1 (0.2)
Leukopenia	4 (0.9)	2 (0.4)
Thrombocytopenia	4 (0.9)	5 (1.1)
Gastrointestinal Disorders		
Nausea	10 (2.4)	12 (2.6)
Diarrhea	9 (2.1)	14 (3.1)
Vomiting	7 (1.6)	5 (1.1)
Abdominal pain	4 (0.9)	3 (0.7)
Dyspepsia	3 (0.7)	1 (0.2)
Constipation	1 (0.2)	3 (0.7)
Hiccups	1 (0.2)	3 (0.7)
Abdominal pain upper	0	3 (0.7)
General Disorders and Administrative Site Conditions		
Pyrexia	4 (0.9)	5 (1.1)
Mycosal inflammation	1 (0.2)	3 (0.7)
Rigors	1 (0.2)	5 (1.1)
Fatigue	0	5 (1.1)
Hepatobiliary Disorders		
Hyperbilirubinemia	12 (2.8)	11 (2.4)
Laboratory Tests		
Alanine aminotransferase increased	4 (0.9)	9 (2.0)
Aspartate aminotransferase increased	3 (0.7)	9 (2.0)
Liver function tests abnormal	3 (0.7)	6 (1.3)
Blood creatinine increased	1 (0.2)	3 (0.7)
Drug level increased	1 (0.2)	3 (0.7)
Transaminases increased	1 (0.2)	4 (0.9)
Metabolism and Nutrition Disorders		
Hypokalemia	8 (1.9)	8 (1.8)
Hypophosphatemia	6 (1.4)	4 (0.9)
Hypomagnesemia	5 (1.2)	6 (1.3)
Hypocalcemia	4 (0.9)	4 (0.9)
Appetite decreased	3 (0.7)	0
Nervous System Disorders		
Headache	4 (0.9)	4 (0.9)
Dysgeusia	3 (0.7)	1 (0.2)
Dizziness	0	5 (1.1)
Skin and Subcutaneous Tissue Disorders		
Rash	6 (1.4)	4 (0.9)
Pruritus	4 (0.9)	3 (0.7)

Vascular Disorders		
Flushing	1 (0.2)	6 (1.3)
Hypotension	1 (0.2)	4 (0.9)

336 Patient base: all randomized patients who received at least 1 dose of trial drug

337 Common: $\geq 0.5\%$ in either treatment arm.

338 *Relationship to drug was determined by the investigator to be possibly, probably, or definitely
339 drug-related.

340 ⁽¹⁾ Within a system organ class patients may experience more than 1 adverse event.

341

342 **Overall MYCAMINE Safety Experience**

343 The overall safety of MYCAMINE was assessed in 1980 patients and
344 422 volunteers in 32 clinical studies, including the esophageal candidiasis and
345 prophylaxis studies, who received single or multiple doses of MYCAMINE,
346 ranging from 12.5 mg to ≥ 150 mg/day.

347

348 A total of 606 subjects (patients and volunteers) received at least 150 mg/day
349 MYCAMINE for a minimum of 10 days.

350

351 Overall, 2028 of 2402 (84.4%) subjects who received MYCAMINE experienced
352 an adverse event. Adverse events considered to be drug-related were reported in
353 717 (29.9%) subjects. Drug-related adverse events which occurred in $\geq 0.5\%$ of
354 all subjects who received MYCAMINE in these trials are shown in Table 4.

Table 4: Common Drug-Related* Adverse Events in Subjects† Who Received MYCAMINE in Clinical Trials

Adverse Events ⁽¹⁾ (MedDRA System Organ Class and Preferred Term)	MYCAMINE n (%)
Number of Patients	2402
Blood and Lymphatic System Disorders	
Leukopenia	38 (1.6)
Neutropenia	29 (1.2)
Thrombocytopenia	20 (0.8)
Anemia	19 (0.8)
Gastrointestinal Disorders	
Nausea	67 (2.8)
Vomiting	58 (2.4)
Diarrhea	38 (1.6)
Abdominal pain	23 (1.0)
Abdominal pain upper	11 (0.5)
General Disorders and Administration Site Conditions	
Pyrexia	37 (1.5)
Rigors	23 (1.0)
Injection site pain	21 (0.9)
Hepatobiliary Disorders	
Hyperbilirubinemia	25 (1.0)
Laboratory Tests	
Aspartate aminotransferase increased	64 (2.7)
Alanine aminotransferase increased	62 (2.6)
Blood alkaline phosphatase increased	48 (2.0)
Liver function tests abnormal	36 (1.5)
Blood creatinine increased	14 (0.6)
Blood urea increased	12 (0.5)
Blood lactate dehydrogenase increased	11 (0.5)
Metabolism and Nutrition Disorders	
Hypokalemia	28 (1.2)
Hypocalcemia	27 (1.1)
Hypomagnesemia	27 (1.1)
Nervous System Disorders	
Headache	57 (2.4)
Dizziness	16 (0.7)
Somnolence	12 (0.5)
Skin and Subcutaneous Tissue Disorders	
Rash	38 (1.6)
Pruritus	18 (0.7)
Vascular Disorders	
Phlebitis	39 (1.6)
Hypertension	14 (0.6)
Flushing	12 (0.5)

357 Patient base: all randomized patients who received at least 1 dose of trial drug
358 Common: Incidence of adverse event $\geq 0.5\%$.
359 *Relationship to drug was determined by the investigator to be possibly, probably, or definitely
360 drug-related.
361 †Subjects included patients and volunteers
362 ⁽¹⁾Within a system organ class, patients may experience more than 1 adverse event
363

364 Other clinically significant adverse events regardless of causality which occurred
365 in these trials are listed below:

366

- 367 • *Blood and lymphatic system disorders:* coagulopathy, hemolysis,
368 hemolytic anemia, pancytopenia, thrombotic thrombocytopenic purpura
- 369 • *Cardiac disorders:* arrhythmia, cardiac arrest, cyanosis, myocardial
370 infarction, tachycardia
- 371 • *Hepatobiliary disorders:* hepatocellular damage, hepatomegaly, jaundice,
372 hepatic failure
- 373 • *General disorders and administration site conditions:* injection site
374 thrombosis
- 375 • *Infections and infestations:* infection, pneumonia, sepsis
- 376 • *Metabolism and nutrition disorders:* acidosis, anorexia, hyponatremia
- 377 • *Musculoskeletal, connective tissue and bone disorders:* arthralgia
- 378 • *Nervous system disorders:* convulsions, encephalopathy, intracranial
379 hemorrhage
- 380 • *Psychiatric disorders:* delirium
- 381 • *Renal and urinary disorders:* anuria, hemoglobinuria, oliguria, renal
382 failure acute, renal tubular necrosis
- 383 • *Respiratory, thoracic and mediastinal disorders:* apnea, dyspnea,
384 hypoxia, pulmonary embolism
- 385 • *Skin and subcutaneous tissue disorders:* erythema multiforme, skin
386 necrosis, urticaria
- 387 • *Vascular disorders:* deep venous thrombosis, hypertension

388

389 **Postmarketing Adverse Events**

390 The following adverse events have been identified during the post-approval use of
391 micafungin sodium for injection in Japan. Because these reactions are reported
392 voluntarily from a population of uncertain size, it is not always possible to
393 reliably estimate their frequency. A causal relationship to micafungin sodium for
394 injection could not be excluded for these adverse events, which included:

- 395 • *Hepatobiliary disorders:* hyperbilirubinemia, hepatic function abnormal,
396 hepatic disorder, hepatocellular damage
- 397 • *Renal and urinary disorders:* acute renal failure and renal impairment
- 398 • *Blood and lymphatic system disorders:* white blood cell count decreased,
399 hemolytic anemia
- 400 • *Vascular disorders:* shock

401

402 **DRUG ABUSE AND DEPENDENCE:**

403 There has been no evidence of either psychological or physical dependence, or
404 withdrawal or rebound effects with MYCAMINE.

405

406 **OVERDOSAGE:**

407 MYCAMINE is highly protein bound and, therefore, is not dialyzable. No cases
408 of MYCAMINE overdose have been reported. Repeated daily doses up to 8
409 mg/kg (maximum total dose of 896 mg) in adult patients have been administered
410 in clinical trials with no reported dose-limiting toxicity. The minimum lethal dose
411 of MYCAMINE is 125 mg/kg in rats, equivalent to 8.1 times the recommended
412 human clinical dose for esophageal candidiasis based on body surface area
413 comparisons.

414

415 **DOSAGE AND ADMINISTRATION:**

416 Do not mix or co-infuse MYCAMINE with other medications. MYCAMINE has
417 been shown to precipitate when mixed directly with a number of other commonly
418 used medications.

419

420 **MYCAMINE DOSAGE**

Indication	Recommended Dose (mg per day)
Treatment of Esophageal Candidiasis ¹	150
Prophylaxis of <i>Candida</i> Infections in HSCT Recipients ²	50

421 ¹In patients treated successfully for esophageal candidiasis, the mean duration of treatment was 15
422 days (range 10-30 days).

423 ²In hematopoietic stem cell transplant (HSCT) recipients who experienced success of prophylactic
424 therapy, the mean duration of prophylaxis was 19 days (range 6-51 days).

425

426 No dosing adjustments are required based on race, gender, or in patients with
427 severe renal dysfunction or mild-to-moderate hepatic insufficiency. The effect of
428 severe hepatic impairment on micafungin pharmacokinetics has not been studied.

429 (See **CLINICAL PHARMACOLOGY – Special Populations.**)

430

431 No dose adjustment for MYCAMINE is required with concomitant use of
432 mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus,
433 nifedipine, fluconazole, ritonavir, or rifampin. (See **PRECAUTIONS – Drug**
434 **Interactions**)

435

436 A loading dose is not required; typically, 85% of the steady-state concentration is
437 achieved after three daily MYCAMINE doses.

438

439 **Directions for Reconstitution and Dilution**

440 Please read this entire section carefully before beginning reconstitution.

441

442 The diluent to be used for reconstitution and dilution is 0.9% Sodium Chloride
443 Injection, USP (without a bacteriostatic agent). Alternatively, 5% Dextrose

444 Injection, USP, may be used for reconstitution and dilution of MYCAMINE.
445 Solutions for infusion are prepared as follows:

446

447 **Reconstitution**

448 MYCAMINE 50 mg vial

449 Aseptically add 5 mL of 0.9% Sodium Chloride Injection, USP (without a
450 bacteriostatic agent) to each 50 mg vial to yield a preparation containing
451 approximately 10 mg micafungin/mL.

452

453 As with all parenteral drug products, reconstituted MYCAMINE should be
454 inspected visually for particulate matter and discoloration prior to administration,
455 whenever solution and container permit. Do not use material if there is any
456 evidence of precipitation or foreign matter. Aseptic technique must be strictly
457 observed in all handling since no preservative or bacteriostatic agent is present in
458 MYCAMINE or in the materials specified for reconstitution and dilution.

459

460 **Dissolution**

461 To minimize excessive foaming, GENTLY dissolve the MYCAMINE powder by
462 swirling the vial. **DO NOT VIGOROUSLY SHAKE THE VIAL.**

463 Visually inspect the vial for particulate matter.

464

465 **Dilution**

466 The diluted solution should be protected from light. It is not necessary to cover
467 the infusion drip chamber or the tubing.

468

469 For prophylaxis of *Candida* infections: add 50 mg MYCAMINE reconstituted in
470 5 mL Sodium Chloride Injection, USP (See **Reconstitution**) into 100 mL of 0.9%
471 Sodium Chloride Injection, USP.

472

473 For treatment of esophageal candidiasis: add 150 mg MYCAMINE (from [3] 50
474 mg MYCAMINE vials) reconstituted in 15 mL Sodium Chloride Injection, USP
475 (see **Reconstitution**) into 100 mL of 0.9% Sodium Chloride Injection, USP.

476

477 MYCAMINE is preservative-free. Discard partially used vials.

478

479 **Infusion Volume and Duration**

480 MYCAMINE should be administered by intravenous infusion over the period of 1
481 hour. More rapid infusions may result in more frequent histamine mediated
482 reactions.

483

484 **NOTE: An existing intravenous line should be flushed with 0.9% Sodium**
485 **Chloride Injection, USP, prior to infusion of MYCAMINE.**

486

487 **STORAGE OF MYCAMINE:**

488 The reconstituted product may be stored in the original vial for up to 24 hours at
489 room temperature, 25° C (77° F).

490

491 The diluted infusion should be protected from light and may be stored for up to 24
492 hours at room temperature, 25° C (77° F).

493

494 **HOW SUPPLIED:**

495 MYCAMINE is available in cartons of 10 individually packaged 50 mg single-
496 use vials, coated with a light protective film and sealed with a blue flip-off cap.
497 (NDC 0469-3250-10). Unopened vials of lyophilized material must be stored at
498 room temperature, 25° C (77° F); excursions permitted to 15°-30°C (59°-86°F).

499 [See USP Controlled Room Temperature.]

500

501 **ANIMAL TOXICOLOGY:**

502 High doses of micafungin sodium have been associated with irreversible changes
503 to the liver when administered for prolonged periods. In a 13-week intravenous
504 rat study (dosed to 5-times clinical exposure, based on body surface area
505 comparisons), with four- or 13-week recovery periods, colored patches/zones,
506 multinucleated hepatocytes and altered cell foci remained at the end of the
507 recovery period. In a similar 13-week intravenous dog study with 4-week
508 recovery (doses to 10 times clinical exposure), liver discoloration, cellular
509 infiltration and hypertrophy remained visible at the end of the 13-week recovery
510 period.

511

512 **CLINICAL STUDIES:**

513

514 **Treatment of Esophageal Candidiasis**

515 In two controlled trials involving 763 patients with esophageal candidiasis, 445
516 adults with endoscopically-proven candidiasis received MYCAMINE, and 318
517 received fluconazole for a median duration of 14 days (range 1-33 days).

518

519 MYCAMINE was evaluated in a phase 3, randomized, double-blind study which
520 compared MYCAMINE 150 mg/day (n=260) to intravenous fluconazole 200
521 mg/day (n=258) in adults with endoscopically-proven esophageal candidiasis.
522 Most patients in this study had HIV infection, with CD4 cell counts <100
523 cells/mm³. Outcome was assessed by endoscopy and by clinical response at the
524 end of treatment. Endoscopic cure was defined as endoscopic grade 0, based on a
525 scale of 0-3. Clinical cure was defined as complete resolution in clinical
526 symptoms of esophageal candidiasis (dysphagia, odynophagia, and retrosternal
527 pain). Overall therapeutic cure was defined as both clinical and endoscopic cure.
528 Mycological eradication was determined by culture, and by histological or
529 cytological evaluation of esophageal biopsy or brushings obtained endoscopically
530 at the end of treatment. As shown in Table 5, endoscopic cure, clinical cure,
531 overall therapeutic cure, and mycological eradication were comparable for
532 patients in the MYCAMINE and fluconazole treatment groups.

533
534
535

Table 5: Endoscopic, Clinical, and Mycological Outcomes for Esophageal Candidiasis at End-of-Treatment

Treatment Outcome*	MYCAMINE 150 mg/day N=260	Fluconazole 200 mg/day N=258	% Difference† (95% CI)
Endoscopic Cure	228 (87.7%)	227 (88.0%)	-0.3% (-5.9, +5.3)
Clinical Cure	239 (91.9%)	237 (91.9%)	0.06% (-4.6, +4.8)
Overall Therapeutic Cure	223 (85.8%)	220 (85.3%)	0.5% (-5.6, +6.6)
Mycological Eradication	141/189 (74.6%)	149/192 (77.6%)	-3.0% (-11.6, +5.6)

536 *Endoscopic and clinical outcome were measured in modified intent-to-treat population, including
537 all randomized patients who received ≥ 1 dose of study treatment. Mycological outcome was
538 determined in the per protocol (evaluable) population, including patients with confirmed
539 esophageal candidiasis who received at least 10 doses of study drug, and had no major protocol
540 violations.

541 †calculated as MYCAMINE – fluconazole

542

543 Most patients (96%) in this study had *Candida albicans* isolated at baseline. The
544 efficacy of MYCAMINE was evaluated in less than 10 patients with *Candida*
545 species other than *C. albicans*, most of which were isolated concurrently with *C.*
546 *albicans*.

547

548 Relapse was assessed at 2 and 4 weeks post-treatment in patients with overall
549 therapeutic cure at end of treatment. Relapse was defined as a recurrence of
550 clinical symptoms or endoscopic lesions (endoscopic grade > 0). There was no
551 statistically significant difference in relapse rates at either 2 weeks or through 4
552 weeks post-treatment for patients in the MYCAMINE and fluconazole treatment
553 groups, as shown in Table 6.

554

555
556

Table 6: Relapse of Esophageal Candidiasis at Week 2 and through Week 4 Post-Treatment in Patients with Overall Therapeutic Cure at the End of Treatment

Relapse	MYCAMINE 150 mg/day N=223	Fluconazole 200 mg/day N=220	% Difference* (95% CI)
Relapse [†] at Week 2	40 (17.9%)	30 (13.6%)	4.3% (-2.5, 11.1)
Relapse [†] Through Week 4 (cumulative)	73 (32.7%)	62 (28.2%)	4.6% (-4.0, 13.1)

557
558
559
560
561

*calculated as MYCAMINE – fluconazole; N=number of patients with overall therapeutic cure (both clinical and endoscopic cure at end-of-treatment); †Relapse included patients who died or were lost to follow-up, and those who received systemic anti-fungal therapy in the post-treatment period

562
563
564
565
566
567
568
569
570
571
572
573
574

In this study, 459 of 518 (88.6%) patients had oropharyngeal candidiasis in addition to esophageal candidiasis at baseline. At the end of treatment 192/230 (83.5%) MYCAMINE treated patients and 188/229 (82.1%) of fluconazole treated patients experienced resolution of signs and symptoms of oropharyngeal candidiasis. Of these, 32.3% in the MYCAMINE group, and 18.1% in the fluconazole group (treatment difference = 14.2%; 95% confidence interval [5.6, 22.8]) had symptomatic relapse at 2 weeks post-treatment. Relapse included patients who died or were lost to follow-up, and those who received systemic antifungal therapy during the post-treatment period. Cumulative relapse at 4 weeks post-treatment was 52.1% in the MYCAMINE group and 39.4% in the fluconazole group (treatment difference 12.7%, 95% confidence interval [2.8, 22.7]).

575
576

Prophylaxis of *Candida* Infections in Hematopoietic Stem Cell Transplant Recipients

577
578
579
580
581

In a randomized, double-blind study, MYCAMINE (50 mg IV once daily) was compared to fluconazole (400 mg IV once daily) in 882 patients undergoing an autologous or syngeneic (46%) or allogeneic (54%) stem cell transplant. The status of the patients' underlying malignancy at the time of randomization was: 365 (41%) patients with active disease, 326 (37%) patients in remission, and

582 195 (22%) patients in relapse. The more common baseline underlying diseases in
583 the 476 allogeneic transplant recipients were: chronic myelogenous leukemia
584 (22%), acute myelogenous leukemia (21%), acute lymphocytic leukemia (13%),
585 and non-Hodgkin's lymphoma (13%). In the 404 autologous and syngeneic
586 transplant recipients the more common baseline underlying diseases were:
587 multiple myeloma (37.1%), non-Hodgkin's lymphoma (36.4%), and Hodgkin's
588 disease (15.6%). During the study, 198 of 882 (22.4%) transplant recipients had
589 proven graft-versus-host disease; and 475 of 882 (53.9%) recipients received
590 immunosuppressive medications for treatment or prophylaxis of graft-versus-host
591 disease.

592

593 Study drug was continued until the patient had neutrophil recovery to an absolute
594 neutrophil count (ANC) of ≥ 500 cells/mm³ or up to a maximum of 42 days after
595 transplant. The average duration of drug administration was 18 days (range 1 to
596 51 days).

597

598 Successful prophylaxis was defined as the absence of a proven, probable, or
599 suspected systemic fungal infection through the end of therapy (usually 18 days),
600 and the absence of a proven or probable systemic fungal infection through the end
601 of the 4-week post-therapy period. A suspected systemic fungal infection was
602 diagnosed in patients with neutropenia (ANC < 500 cells/mm³); persistent or
603 recurrent fever (while ANC < 500 cells/mm³) of no known etiology; and failure to
604 respond to at least 96 hours of broad spectrum antibacterial therapy. A persistent
605 fever was defined as four consecutive days of fever greater than 38°C. A
606 recurrent fever was defined as having at least one day with temperatures ≥ 38.5 °C
607 after having at least one prior temperature > 38 °C; or having two days of
608 temperatures > 38 °C after having at least one prior temperature > 38 °C.
609 Transplant recipients who died or were lost to follow-up during the study were
610 considered failures of prophylactic therapy.

611

612 Successful prophylaxis was documented in 80.7% of recipients who received
 613 MYCAMINE, and in 73.7% of recipients who received fluconazole (7.0%
 614 difference [95% CI = 1.5, 12.5]), as shown in Table 7, along with other study
 615 endpoints. The use of systemic antifungal therapy post-treatment was 42% in both
 616 groups.

617

618 The number of proven breakthrough *Candida* infections was 4 in the
 619 MYCAMINE and 2 in the fluconazole group.

620

621 The efficacy of MYCAMINE against infections caused by fungi other than
 622 *Candida* has not been established.

623

624 **Table 7: Results from Clinical Study of Prophylaxis of *Candida* Infections in Hematopoietic**
 625 **Stem Cell Transplant Recipients**

Outcome of Prophylaxis	MYCAMINE 50 mg/day (n=425)	Fluconazole 400 mg/day (n=457)
Success *	343 (80.7%)	337 (73.7%)
Failure:	82 (19.3%)	120 (26.3%)
All Deaths ¹	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/probable fungal infection (not resulting in death) ¹	6 (1.4%)	8 (1.8%)
Suspected fungal infection ²	53 (12.5%)	83 (18.2%)
Lost to follow-up	5 (1.2%)	3 (0.7%)

626 * Difference (MYCAMINE – Fluconazole): +7.0% [95% CI=1.5, 12.5]

627 ¹ Through end-of-study (4 weeks post- therapy)

628 ² Through end-of-therapy

629

630

631 **Rx only**

632

633 **Manufactured for:**

634 Fujisawa Healthcare, Inc.

635 Deerfield, IL 60015-2548

636

637 March 2005

638

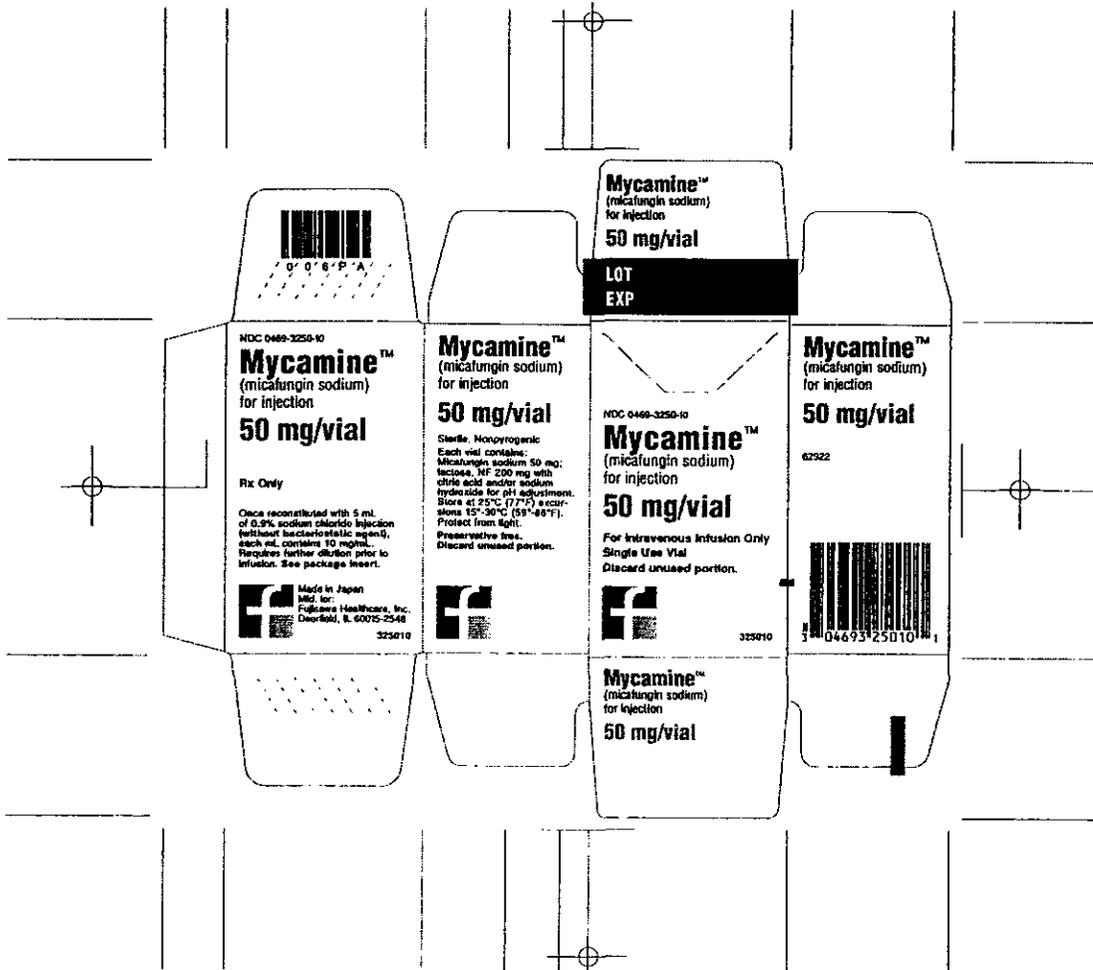
639

640 MYCAMINE is a trademark of Fujisawa Pharmaceutical Company Ltd., Osaka,

641 Japan.

642

643



PMS-186C PMS-186C PMS-301C Black PMS-300C

Sep. 05, 2002
Revised by I.Horii/Fujisawa Japan

CrossTech-C45422-Proof 1
Form M03-PS:C1
Fujisawa-P.O. 21321-Job No. 62922
3/10/05-jc-Q4.11

Fonts: Helvetica (A)

CrossTech
COMMUNICATIONS INC

312 382-0111 FAX 382-0004

NDC 0489-3250-10

Mycamine™
(micafungin sodium)
for injection

50 mg/vial

50 mg X 10 Vials

325010



NDC 0489-3250-10

Mycamine™
(micafungin sodium)
for injection
For Intravenous Infusion Only

50 mg/vial

Once reconstituted with 5 mL of 0.9% sodium chloride injection
(without bacteriostatic agent), each mL contains 10 mg/mL.
Requires further dilution prior to infusion. See package insert.

Single Use Vial. Discard unused portion.

Rx Only
50 mg X 10 Vials

325010



Mycamine™
(micafungin sodium)
for injection
50 mg/vial

Made in Japan
Mfg. for:
Fujisawa Healthcare, Inc.
Deerfield, IL 60015-0548
50 mg X 10 Vials



NDC 0489-3250-10

Mycamine™
(micafungin sodium)
for injection
For Intravenous Infusion Only

50 mg/vial

Stable, Nonpyrogenic
Each vial contains: Micafungin sodium 50 mg;
lactose, NF 200 mg with citric acid and/or sodium
hydroxide for pH adjustment.
Store at 20°C (77°F); excursions 15°-30°C (59°-86°F).
(See USP Controlled Room Temperature) Protect from light.

50 mg X 10 Vials

325010



(1) 2 0304893 23010 5



Mycamine™
(micafungin sodium)
for injection
50 mg/vial

Preservative free. Discard unused portion.

50 mg X 10 Vials



Mycamine™
(micafungin sodium)
for injection
50 mg/vial

50 mg X 10 Vials

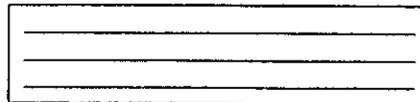
62923

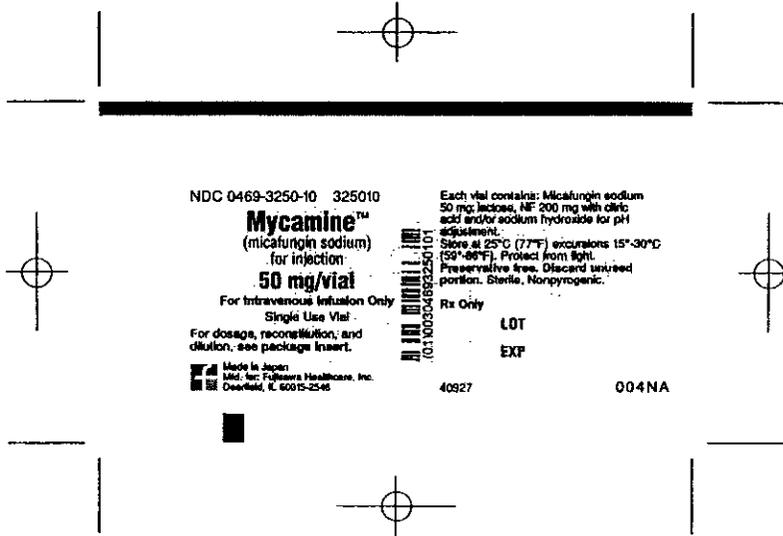
PMS-196C PMS-197C PMS-201C PMS-200C Black

CrossTech-C45421-Proof 1
Form M03-PS-C1
Fujisawa-P.O. 21321-Job No. 62923
3/10/05-jc-Q4.11

Fonds: Helvecos SA

CrossTech
COMMUNICATIONS INC
312.342.0111 FAX 312.342.0004





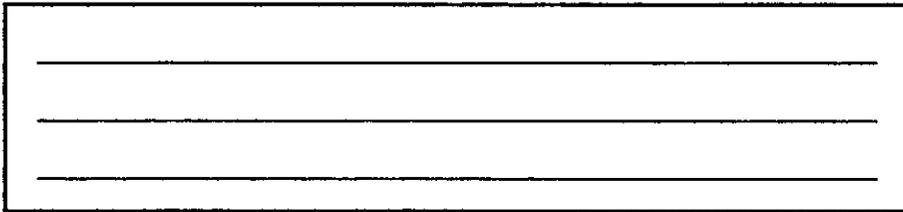
PMS-186C

PMS-116C

PMS-301C

PMS-300C

Black



CrossTech-B45420-Proof A7
Form M01-PS:B1
Fujisawa-P.O. 21321-Job No. 40927
2/24/05-hc-Q4.11

Fonts: Helvetica (A)
Typesmiths Pi Font

CrossTech
COMMUNICATIONS INC

312 382-0111  FAX 382-0004

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Edward Cox
3/16/05 12:54:49 PM
for Mark J. Goldberger, MD MPH