

The Applicant's overall clinical, microbiological, and therapeutic cure rates for patients evaluable for overall efficacy (evaluable at RV1 and RV2) are presented in Table 21a.

Table 21a. Summary of the Applicant's Overall Cure Rates by Treatment Group, Patients Valid for Overall Efficacy

Type of Cure	Treatment Group				P-value*
	Miconazole Nitrate (1200 mg) Vaginal [REDACTED] N= 99		MONISTAT®7 Vaginal Cream N=97		
	n	%	n	%	
Clinical	81	81.8	79	81.4	0.96
Microbiological	75	75.8	71	73.2	
Therapeutic	71	71.7	68	70.1	

*The Cochran-Mantel-Haenszel Test, stratified by investigator, was used to detect any difference between the treatment groups.

(Applicant's Table V, from Vol. 1.9, p. 08-000206)

In order to investigate the comparability in the overall clinical, microbiological, and therapeutic cure rates, the Applicant calculated 95% confidence intervals for the difference in the point estimates of the cure rates (Table 21b).

Table 21b. Difference in the Applicant's Overall Cure Rates and 95% Confidence Intervals for Patients Evaluable for Overall Efficacy

Response	Point Estimate of the Difference in Cure Rates*	95% Confidence Limits of the Difference in Cure Rates*
Clinical	0%	(-10%, 11%)
Microbiological	3%	(-10%, 15%)
Therapeutic	2%	(-11%, 14%)

*The difference is miconazole nitrate 1200 mg [REDACTED] minus MONISTAT®7

(Table adapted from the Applicant's data tabulation Vol. 1.9, p. 08-000243)

The point estimate of the differences in the Applicant's overall clinical, microbiological, and therapeutic cure rates are contained within their respective 95% confidence interval and are all within the lower bound of -20% as specified by the delta. Therefore, the overall cure rates support statistical similarity between the treatment groups.

MO Comment: The statistical reviewer, Dr. Cheryl Dixon, performed a modified intent-to-treat (MITT) analysis in order to evaluate efficacy in this population. The MITT population was defined as all randomized patients with a positive KOH smear and BiGGY culture at baseline. The results of her MITT analysis found the 1200 mg [REDACTED] to be statistically similar to MONISTAT®7 with regards to clinical, microbiological, and

therapeutic response rates overall (Table 22). Please see the Dr. Dixon's Review for details of the analysis.

Table 22. FDA Statistician's Overall Clinical, Microbiological, and Therapeutic Cure Rates by Modified Intent-to-Treat Analysis for Study 96-002

Type of Cure N(%)	1200 mg N = 120	M7C N = 129	Corrected 95% CI
Clinical	85 (71%)	91 (71%)	(-12%, 12%)
Microbiological	79 (66%)	83 (64%)	(-11%, 14%)
Therapeutic	74 (62%)	77 (60%)	(-11%, 14%)

MO Efficacy Analysis

The MO performed an analysis to examine clinical, microbiological, and therapeutic efficacy in the subset of the Applicant's evaluable patients whose visits occurred within the protocol specified visit windows or in a second analysis within ± 2 days of the protocol specified windows. The analyses were performed using the Applicant's assessments of cure, failure, and indeterminate. The following criteria were used to perform the analyses.

For the analysis of cure rates at RV1

1. A patient's RV1 must occur within Study Days 15-19 inclusive
2. If the patient was declared a failure prior to the specified RV1 window, the patient is included in the analysis as a failure.
3. If a patient's RV1 occurred after Study Day 19, the patient was not included in the analysis regardless of whether the patient was scored as cure, indeterminate, or failure.

For analysis of overall cure rates

1. Patients must meet all of the above criteria for RV1
2. RV2 must occur within Study Days 35-43
3. Patients whose RV2 assessment occurred prior to the specified RV2 window and who were scored as failures were included in the analysis.
4. If a patient's RV2 occurred after Study Day 43, the patient was not included in the analysis regardless of whether the patient was scored as cure, indeterminate, or failure.

A second analysis was performed using the rules above but allowing the protocol specified RV1 and RV2 windows to be widened by ± 2 days.

The results of the MO's analyses are presented for the clinical cure rates, microbiological cure rates, and for the therapeutic (composite clinical and microbiological results) cure rates (Tables 23a-c).

Table 23a. MO's Clinical Cure Rates by Visit Window

Visit Window	Cure Rate by Treatment Group				Difference in Cure Rates	95% CI*
	1200 mg [REDACTED]		MONISTAT® Cream			
	n/N	%	n/N	%		
Cure Rate at RV1						
RV 1 (Day 15-19)	84/90	93	88/91	97	-3	(-11, 4)
RV 1 ± 2 days (Day 13-21)	97/104	93	95/98	97	-3	(-10, 3)
Overall Cure Rate						
RV 1 (Day 15-19) & RV 2 (Day 35-43)	64/72	89	67/79	85	4	(-8, 16)
RV 1 ± 2 days (Day 13-21) & RV 2 ± 2 days (Day 33-45)	77/88	88	74/87	85	3	(-9, 14)

Table 23b. MO's Microbiological Cure Rates by Visit Window

Visit Window	Cure Rate by Treatment Group				Difference in Cure Rates	95% CI*
	1200 mg [REDACTED]		MONISTAT® Cream			
	n/N	%	n/N	%		
Cure Rate at RV1						
RV 1 (Day 15-19)	79/90	88	84/91	92	-4	(-14, 5)
RV 1 ± 2 days (Day 13-21)	92/104	88	90/98	92	-4	(-12, 6)
Overall Cure Rate						
RV 1 (Day 15-19) & RV 2 (Day 35-43)	61/78	78	60/84	71	7	(-8, 21)
RV 1 ± 2 days (Day 13-21) & RV 2 ± 2 days (Day 33-45)	73/95	77	68/94	72	5	(-9, 18)

Table 23c. MO's Therapeutic Cure Rates by Visit Window

Visit Window	Cure Rates by Treatment Group				Difference in Cure Rates	95% CI*
	1200 mg [REDACTED]		MONISTAT® Cream			
	n/N	%	n/N	%		
Cure Rate at RV1						
RV 1 (Day 15-19)	76/90	84	82/91	90	-6	(-16, 5)
RV 1 ± 2 days (Day 13-21)	88/104	85	88/98	90	-5	(-15, 5)
Overall Cure Rate						
RV 1 (Day 15-19) & RV 2 (Day 35-43)	58/79	73	57/84	68	5	(-10, 21)
RV 1 ± 2 days (Day 13-21) & RV 2 ± 2 days (Day 33-45)	70/97	72	65/94	69	3	(-11, 17)

*The 95% confidence intervals with a continuity correction were calculated by the Agency's Statistical Reviewer, Dr. Cheryl Dixon.

MO Comment: The differences in denominators at RV2 are secondary to failures being carried forward and patients who were discontinued after being declared failures at RV1. For example, a patient who was declared a microbiological failure and a clinical cure at RV1 would be

scored as a microbiological and therapeutic failure at RV1, meets the criteria for discontinuation from study, and the microbiological and therapeutic failure scores would be carried forward to RV2. However, the cure determination at RV1 is not carried forward and the absence of an RV2 clinical assessment would not allow this patient to be included in the overall clinical response population because of the absence of a clinical outcome assessment at RV2.

The results of the MO's analyses finds the clinical, microbiological, and therapeutic cure rates statistically similar with the lower bound of the confidence interval within the delta of -20%. These analyses using the protocol specified windows for RV1 and RV2 corroborate the findings of the Applicant's efficacy analyses and support that the 1200 mg [REDACTED] (MONISTAT® DUAL-PAK) is therapeutically similar to its comparator (MONISTAT® 7 Vaginal Cream).

Recurrence Rates

The Applicant also investigated recurrence rates by examining the proportion of patients who developed clinical or microbiological evidence of VVC at RV2 who had previously been assessed as overall therapeutic cures at RV1 (Table 24).

Table 24. Recurrence Rates at Return Visit 2 for Patients Assessed as Overall Therapeutic Cures at Return Visit 1 (per Applicant).

Response Category	Recurrence Rate by Treatment Group			
	1200 mg [REDACTED] (N = 82)*		MONISTAT®7 Vaginal Cream (N = 87)*	
	(n/N)	(%)	(n/N)	(%)
Clinical	4/82	4.9	9/87	10.3
Microbiological	10/82	12.2	17/87	19.5
Therapeutic	10/82	12.2	17/87	19.5

(Table derived from the Applicant's Table VI, Vol. 1.9, p. 08-000208)

* Note the denominator for recurrence rate is the number of patients who are Therapeutic cures at RV1 for each of the treatment arms and valid for overall efficacy

The overall recurrence rates are comparable for the two treatment groups.

MO Comment: In this study (study 96-002) the organisms obtained on BiGGY culture were not speciated. Therefore, it is difficult to assess true relapse, the recurrence of the same organism as previously isolated. However, this affects each treatment arm equally. Similarly, without speciation it is not possible to determine if there are certain *Candida* spp. that are less responsive to therapy.

The Applicant analyzed overall therapeutic cure rates based on disease severity (Table 25).

Table 25. Overall Therapeutic Cure Rate by Disease Severity (per Applicant)

Disease Severity	Overall Therapeutic Cure Rate			
	1200 mg ██████ (N = 99)		MONISTAT®7 Vaginal Cream (N = 97)	
	n/N	%	n/N	%
Very Mild	3/3	100	0/1	0
Mild	44/61	72	40/53	76
Moderate	19/30	63	23/35	66
Severe	5/5	100	5/8	63

(Adapted from Applicant's table 8, Vol. 1.9 p. 08-000234)

Most of the patients in the study had disease of either mild or moderate severity. Although the number of patients with severe disease is small, the limited data show cure rates comparable to the overall therapeutic cure rates for the study. The Applicant performed a Cochran-Mantel-Haenszel (CMH) test on the distribution of cure rate by disease severity stratified by treatment group. The CMH test did not demonstrate a significant difference in cure rate by disease severity ($p = 0.390$).

The overall therapeutic cure rates by race were examined for each of the treatment groups (Table 26)

Table 26. Overall Therapeutic Cure Rate by Race (per Applicant)

Race	Overall Therapeutic Cure Rate			
	1200 mg ██████ (N = 99)		MONISTAT®7 Vaginal Cream (N = 97)	
	n/N	%	n/N	%
Caucasian	43/57	75	43/57	75
Black	8/13	62	7/15	47
Hispanic	16/24	67	13/19	68
Other	4/5	80	5/6	83

(Adapted from Applicant's table 9, Vol. 1.9 p. 08-000235)

The overall therapeutic cure rates by race for each of the treatment groups are comparable (considering the small number of patients in some of the strata). The Applicant calculated a CMH test for overall therapeutic cure rate by race stratified by treatment group and did not find a significant difference in cure rates for different races ($p = 0.110$).

The overall therapeutic cure rates by age were examined by stratifying the patients into five 10-year age strata (Table 27).

Table 27. Overall Therapeutic Cure Rate by Age Group (per Applicant)

Age Group	Overall Therapeutic Cure Rate			
	1200 mg ██████ (N = 99)		MONISTAT®7 Vaginal Cream (N = 97)	
	n/N	%	n/N	%
18-27	31/41	76	27/42	64
28-37	11/16	69	18/21	86
38-47	17/22	77	13/21	62
48-57	10/15	67	5/7	71
>57	2/5	40	5/6	83

(Adapted from Applicant's table 10a, Vol. 1.9 p. 08-000236)

The overall therapeutic cure rates for each of the age groups are comparable across age groups (given the limited number of observations in some age groups). The Applicant performed a CMH test on the overall therapeutic cure rate by age group stratified by treatment group and did not find a significant difference in the overall therapeutic cure rate by ten-year age group ($p = 0.833$). The same was also true when the Applicant looked at the age groups of ≤ 45 years vs. ≥ 46 years.

MO Comment: A total of 8 patients 65 years and over were enrolled in study 96-002 (1200 mg ██████ (3), MONISTAT®7 (5)). The proportion of patients 65 years of age and older valid for overall efficacy classified as overall therapeutic cures was 1/2 in the 1200 mg ██████ group and 4/5 in the MONISTAT®7 group.

The Applicant also looked at the effect of the following covariables on overall therapeutic cure rates within treatment groups in patients valid for overall efficacy:

- intercourse and condom use between admission and Return Visit 1
- intercourse and condom use between Return Visit 1 and Return Visit 2
- oral contraceptive usage

The only finding that was statistically significant was the effect on cure rate within a treatment group of intercourse and inconsistent condom use between RV1 and RV2. This finding was further investigated by comparing the cure rates between treatment groups stratifying the data by condom use. No statistically significant covariate effect on the difference in cure rate between treatment group was found when the data were stratified by condom use ($p = 0.29$).

The Applicant analyzed the secondary variable of time to relief of symptoms by examining

- days to relief of vulvovaginal itching and burning/irritation (days 1-8)
- proportion of patients reporting no itching and no burning at RV1

- proportion of patients who reported itching or burning at RV1, but no itching or burning at RV2
- proportion of patients who reported itching or burning at RV1 and data for RV2 missing
- proportion of patients reported itching or burning at both RV1 and RV2
- proportion of patients who reported no itching or burning at Admission and RV1

The Applicant presents the following data for days to relief of itching and burning (Table 28). This endpoint is defined as the first day that relief is achieved for both itching and burning/irritation.

Table 28. Cumulative Days to Relief of Itching and Burning/Irritation, Patients Valid for Overall Efficacy

Group	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
OVULE N = 94*	10 10.6%	29 30.9%	40 42.6%	49 52.1%	60 63.8%	66 70.2%
M7C N = 92*	9 9.8%	15 16.3%	33 35.9%	42 45.7%	55 59.8%	64 69.6%

* = patients exhibiting symptoms at admission

(Applicant's Table VIII from Vol. 1.9, p. 08-000210)

The Applicant notes that the proportion of patients meeting the criteria for the relief of itching and burning when compared at Day 3 is different between the two treatment groups ($p = 0.025$). The Applicant also notes that the median time to relief of symptoms is 4 days for the 1200 mg [REDACTED] and 5 days for MONISTAT®7.

MO Comment: The study was not designed to test hypotheses with regards to the secondary variable of time to relief of symptoms defined *post hoc*. These results should be interpreted with caution since they represent analyses defined *post hoc*. In addition, the comparison of multiple time points in the above *post hoc* analysis may lead to an inflated Type I error.

The data that the Applicant cites for Day 3 appears to be the only day for which there is a significant difference between the two treatment groups. Given the variability as to the time of administration of the medication, the time of recording of symptoms, and the subjectivity of the measure, one must question the precision of the methods employed to measure such a transient finding.

Given that the study was not designed to assess time to relief of symptoms, the analysis of these secondary variables were defined

post hoc, the methods used were not precise enough to reliably measure a difference on a given Study Day, the multiple analyses performed may result in an elevated Type I error, the information that the Applicant presents regarding time to relief of symptoms should be interpreted with caution. It is also unclear that this isolated finding on Day 3 is clinically meaningful.

Microbiology

At the time of admission to the study patients were evaluated with a KOH smear and a BiGGY vaginal culture to confirm the presence of *Candida* sp. The culture isolates were not speciated.

The microbiological response rates are discussed in the clinical efficacy section.

MO Comment: Given the absence of information on speciation of the mycologic isolates, efficacy of the treatments with regards to the particular *Candida* species cannot be performed in this study.

Safety

All patients who received study medication and for whom safety data was available were analyzed for safety. A total of 12 (6 from each arm of the study) of the 278 patients enrolled did not provide safety data. One of the 12 patients did not use study medication and 11 were lost to follow-up without providing any safety information.

In the patients evaluable for safety, satisfactory medication compliance was achieved in 95% (127/134) of patients using the 1200 mg [REDACTED] and 92% (122/132) of the patients using MONISTAT[®]7. Seven patients using the ovule were classified as non-compliant because the date that they used the ovule was unknown. The 10 patients using MONISTAT[®]7 were classified as non-compliant because they skipped more than one day or dose of treatment (4), used an unknown number of doses or days of therapy (4), or delayed the start of treatment more than two days (2).

The total number of adverse events reported was 264 in 100 out of the 134 (75%) patients in the 1200 mg [REDACTED] group and 234 in 84 out of the 132 (64%) patients in the MONISTAT[®]7 arm.

The Applicant tabulated the number of patients experiencing an adverse event by body system, frequently occurring adverse events, and adverse experiences reported by 2 to 5% of patients (Table 29).

Table 29. Body Systems with the Highest Incidence of Adverse Experiences, All Causality (Greater than 10% in Either Treatment Group)

Body System	Treatment Group			
	MCN (1200 mg) Vaginal (N = 134)		MONISTAT [®] 7 (2% MCN) Vaginal Cream (N = 132)	
	n	%	n	%
Genital/reproductive system	67	50.0	54	40.9
Nervous system	35	26.1	36	27.3
Respiratory system	17	12.7	20	15.2
Gastrointestinal system	25	18.7	11	8.3

(Applicant's table IX from Vol. 1.9, p. 08-000212)

MO Comment: A greater proportion of patients in the 1200 mg [REDACTED] group reported adverse experiences involving the genital and reproductive system. Table 33 provides further details of selected adverse experiences involving the genital and reproductive system.

MO Comment: A greater number of patients with adverse experiences (AEs) involving the gastrointestinal system were reported in the 1200 mg [REDACTED] group. The MO reviewed AEs involving the gastrointestinal system to examine any patterns that might account for the observed differences. Table 30 below lists the adverse experiences associated with the gastrointestinal system as specified in the Applicant's appendix 7. Note that Table 29 is based on the number of patients experiencing adverse experiences within the gastrointestinal system classification while Table 30 is based on the number of adverse experiences within the gastrointestinal system. Therefore, Table 30 lists 27 gastrointestinal adverse experiences for the 1200 mg [REDACTED] and 12 for MONISTAT[®]7 (vs. 25 and 11 listed in Table 29). The source of the difference is two patients in the 1200 mg [REDACTED] arm with two adverse experiences (Pt. 801 with GI cramps and GI bleeding, and Pt. 1418 with nausea and diarrhea) and one patient in the MONISTAT[®]7 arm with two adverse experiences (Pt. 708 with gastritis and vomiting).

The number of patients experiencing gastrointestinal cramps in the 1200 mg [REDACTED] arm is 8 vs. 3 in the MONISTAT[®]7 arm. The applicant notes that the number of patients reporting dysmenorrhea, an AE that could overlap with similar events classified as gastrointestinal cramps, is reversed between the two treatment groups. The number of patients reporting dysmenorrhea in the 1200 mg [REDACTED] group is 3 vs. 8 in the MONISTAT[®]7 arm.

The number of patients experiencing nausea is 6 in the 1200 mg [REDACTED] group vs. 1 in the MONISTAT®7 arm. One patient in the MONISTAT®7 arm reported vomiting. The significance in the differences of the observed rates given the small number of events is unclear. The remainder of the adverse experiences are infrequent events too small in number to allow meaningful comparisons. Some of the similar categories in Table 30 could be merged but doing so is not likely to change the overall impression of gastrointestinal adverse experiences.

Table 30. Adverse Experiences (AEs) Reported Involving the Gastrointestinal System

Adverse Experience	Treatment Group			
	MCN (1200 mg) Vaginal [REDACTED] (N = 134)		MONISTAT®7 (2% MCN) Vaginal Cream (N = 132)	
	n	(%)	n	(%)
Cramps, GI	8	6.0	3	2.3
Nausea	6	4.5	1	0.8
Diarrhea	2	1.5	2	1.5
Dry Mouth	2	1.5	1	0.8
Dyspepsia	2	1.5	0	0.0
Bleeding, GI	1	0.7	0	0.0
Colitis	1	0.7	0	0.0
Constipation	1	0.7	0	0.0
Distress, GI	1	0.7	1	0.8
Flatulence	1	0.7	0	0.0
Gastritis	0	0.0	1	0.8
Pain, Gastrointestinal	1	0.7	2	1.5
Toothache	1	0.7	0	0.0
Vomiting	0	0.0	1	0.8
TOTAL # of AEs	27	20.1	12	9.8
TOTAL # of Patients w/GI AEs	25	18.7	11	8.3

(Adapted from Appendix 7 pp.11-000638 through 11-000652)

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Table 31. Most Frequently Reported Adverse Experiences by Primary Term, All Causality (Greater than 5% in Either Treatment Group)

Adverse Experience	Treatment Group			
	MCN (1200 mg) Vaginal (N = 134)		MONISTAT [®] 7 (2% MCN) Vaginal Cream (N = 132)	
	n	%	n	%
Pruritus, external female genitalia	30	22.4	35	26.5
Headache	31	23.1	32	24.2
Burning, female genitalia	32	23.9	29	22.0
Irritation, female genitalia	21	15.7	10	7.6
Discharge, female genitalia	16	11.9	4	3.0
Upper respiratory infection	10	7.5	8	6.1
Cramps, GI	8	6.0	3	2.3
Dysmenorrhea	3	2.2	8	6.1

(Applicant's table X from Vol. 1.9, p. 08-000213)

MO Comment: The rates for patients reporting "discharge, female genitalia" are higher in the 1200 mg [REDACTED] arm of the study. The significance of the excess of patients reporting discharge is unclear. It could potentially be related to the formulation, the underlying disease (VVC), or chance variation.

MO Comment: The rates for the symptom of burning of the female genitalia are similar for the two treatment groups. However, a higher rate of irritation of the female genitalia is noted in the 1200 mg [REDACTED] group. Querying the Applicant's database reveals a distribution of severity of disease that is comparable between the two groups with a slightly greater proportion of patients with severe irritation in the 1200 mg group (Table 32).

Table 32. Severity of Irritation of the Female Genitalia by Treatment Group

Severity of Irritation, Female Genitalia	1200 mg [REDACTED] (N = 134)		MONISTAT [®] 7 (N = 132)	
	n/N	%	n/N	%
Mild	7/134	33	4/132	40
Moderate	8/134	38	4/132	40
Severe	6/134	29	2/132	20

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The Applicant also looked at the proportion of patients experiencing itching and burning versus itching and burning accompanied by irritation and pain (Table 33).

Table 33. Patients Reporting Selected Groupings of Genital/Reproductive Adverse Experiences

Adverse Experience Grouping	Treatment Group			
	MCN (1200 mg) Vaginal [REDACTED] (N = 134)		MONISTAT [®] 7 (2% MCN) Vaginal Cream (N = 132)	
	n	%	n	%
Itching and Burning	46	34.3	44	33.3
Itching, Burning and Irritation	48	35.8	44	33.3
Itching, Burning, Irritation and Pain	51	38.1	44	33.3

(Applicant's Table XII, Vol. 1.9, p. 08-000214)

MO Comment: The rates for these similar symptoms in Table 33 above are comparable with a slightly greater proportion of patients exhibiting symptoms in the 1200 mg [REDACTED] arm of the study.

Table 34. Adverse Experiences Reported by 2 to 5% (by Primary Term)

Adverse Experience	Treatment Group			
	MCN (1200 mg) Vaginal [REDACTED] (N = 134)		MONISTAT [®] 7 (2% MCN) Vaginal Cream (N = 132)	
	n	%	n	%
Dysuria	5	3.7	4	3.0
Nausea	6	4.5	1	0.8
Pharyngitis	4	3.0	3	2.3
Pain, trunk	3	2.2	4	3.0
Vaginitis	2	1.5	5	3.8
Infection, viral	3	2.2	3	2.3
Pain, female genitalia	5	3.7	0	0.0
Cough	2	1.5	3	2.3
Congestion, respiratory	1	0.7	4	3.0
Insomnia	3	2.2	1	0.8
Rash	1	0.7	3	2.3
Erythema, female genitalia	3	2.2	0	0.0

(Applicant's Table XI, Vol. 1.9, p. 08-000213)

MO Comments: Higher rates for nausea and pain of the female genitalia were observed in the 1200 mg [REDACTED] group. The rates of

vaginitis and respiratory congestion were higher in the MONISTAT[®] 7 arm. Given the small number of events, these differences may represent chance variations.

MO Comment: The MO reviewed and reclassified some of the adverse experiences involving the urinary system. Because of the overlapping nature of the terms used to classify urinary adverse experiences (e.g. cystitis, UTI, urinary tract disorder, frequency, and dysuria) uniform categorization of adverse events was necessary to allow comparison between treatment groups. The Applicant's rates for adverse experiences involving the urinary system are shown in Table 35.

Table 35. Applicant's Rates for Adverse Experiences Involving the Urinary System

Adverse Experience	Treatment Group Study 96-002			
	1200 mg Vaginal [REDACTED] (N = 134)		MONISTAT [®] 7 (N = 132)	
	n/N	%	n/N	%
Dysuria	5/134	3.7	4/132	3.0
Cystitis	1/134	0.7	0/132	0.0
Hematuria	1/134	0.7	0/132	0.0
Frequency, Urinary	0/134	0.0	1/132	0.8
Urinary Tract Disorder, NOS	2/134	1.5	2/132	1.5

(Results summarized from Appendices 7 & 8 in Vol. 1.16)

The MO found that three of the patients in the 1200 mg [REDACTED] arm were treated with antimicrobials for a urinary tract infection. Patient No. 1517 had cystitis and was treated with ciprofloxacin. The adverse events for Patients 1411 and 1101 were classified as urinary tract disorder, NOS, further described on the case report forms as "UTI" and were treated with trimethoprim and norfloxacin respectively. One additional patient not classified as UTI (by the applicant or the MO) (patient 1114) experienced dysuria and was treated with methenamine, phenyl salicylate, atropine sulfate, hyoscyamine, benzoic acid, and methylene blue.

Three patients in the MONISTAT[®] 7 arm were treated with antimicrobials for the urinary tract. The adverse events for Patients 503 and 1311 both classified as urinary tract disorder, NOS were both additionally described in the adverse event tabulations as "UTI." These patients were treated with trimethoprim/ sulfamethoxazole and amoxicillin respectively. Patient 619 had the experience of dysuria and was treated with "urinary anti-infectives." She was therefore also considered as having a UTI. Hence, the MO's rates for "UTI" were 3 events in each arm of the study.

It deserves mention to note the limitations of the MO's criteria to classify a patient as having a UTI. The criteria for UTI are based upon the presence of UTI as the term used to describe the adverse event or the use of a related term(s) for a urinary tract infection or symptom(s) of a urinary tract infection followed by treatment with a conventional antimicrobial agent directed at the urinary tract. This approach represents a best approximation approach based on the data. Also worthy of note is that patients may experience dysuria secondary to inflammation of the urethral opening in the absence of a urinary tract infection.

The Applicant tabulated the summary of findings in patients that were discontinued from the study because of adverse events.

Table 36. Patients Discontinuing Study Due to an Adverse Experience

Patient	Age/ (Race)	Adverse Experience (AE)	Study Day of AE Onset	Severity/ Relation	Action	Outcome
M1200						
00310	28 (C)	Increased & bloody vaginal discharge, vaginal itching, burning & irritation	2	moderate to severe and most probably related	counteractive medications	resolved
00405	23 (C)	vaginal burning, labial swelling, and facial swelling	2	severe/serious and probably or highly probably related	counteractive medications	resolved
M7C						
00114	21 (B)	vaginal burning and swelling	1	severe and possibly related	DC drug	resolved
00819	30 (C)	red itching rash over body and swelling of arms and legs	2	severe and possibly to highly probably related	DC drug and counteractive medications	resolved

(Table adapted from Applicant's Table XIII from Vol. 1.9, p. 08-000215)

The rates of study discontinuation because of an adverse event are similar for the two treatment arms. The Applicant also noted that one patient in each treatment arm was discontinued for a local adverse reaction and one patient in each arm was discontinued for a systemic adverse reaction.

Summaries of the patients discontinued because of an adverse event and a patient with a serious adverse event unrelated to study medication are provided below.

Patient number 00310

The patient was a 28-year-old female with VVC confirmed by a positive 10% KOH preparation and a BiGGY culture. At the admission visit the patient was noted to have moderate itching, burning, and discharge, and severe vulvar and vaginal erythema on examination. She was randomized and reports using the 1200 mg vaginal [REDACTED]. The next day she noted severe vaginal itching and burning, moderate vaginal pain, and increased bloody vaginal discharge graded as severe. Because of increased symptoms, the patient received oral Diflucan®, topical Mycolog®-II cream, and ibuprofen for vaginal pain. Her symptoms were mild by Study Day 4 and had resolved by Study Day 7. On Study Day 15 she was symptom free and had no abnormal findings on gynecologic examination. The patient had no known history of sensitivity to the imidazole class of drugs or intolerance of the components of the ovule or cream formulations. The patient was discontinued from the study for increased vaginal discharge, itching, and burning.

Patient number 00405

The patient was a 23-year-old female with a history of asthma and seasonal allergies. She was admitted to the study with the diagnosis of VVC confirmed with a positive 10% KOH preparation and culture. She was randomized and received the 1200 mg vaginal [REDACTED]. On Study Day 2 she developed labial and facial swelling graded as serious and vaginal burning graded as severe. She also reportedly required catheterization secondary to her labial swelling. She was treated with oral corticosteroids, diphenhydramine, and Lortabs® for relief of her allergic reaction and vaginal burning. Her adverse reaction resolved after 5 days. She returned for a follow-up visit on Study Day 7 and was noted to have no symptoms and only mild vaginal erythema and edema on examination.

Patient number 01015

The patient was a 23-year-old female admitted into the study for VVC with a positive KOH smear. She was randomized to and used the 1200 mg [REDACTED]. She noted absence of itching or burning/irritation at Study Day 2. Subsequently she was noted to have a negative BiGGY culture and was discontinued from study for this reason. The patient had a history of depression, substance abuse, and prior suicide attempts. On Study Day 4 she attempted suicide. This event was considered unrelated to the study medication. She recovered from her adverse experience.

Patient number 00114

The patient was a 21-year-old female with VVC as diagnosed with a positive KOH and culture. She was randomized to MONISTAT®7. The patient's diary indicates medication use on Study Day 1 and no medication use on Study

Days 2,3, or 4. She returned for a follow-up assessment on Study Day 4 and was noted to have worsened symptoms and clinical findings on gynecologic exam. She was discontinued from study because of her adverse experience of worsening symptoms and the development of vulvovaginal edema.

Patient number 00819

The patient was a 30-year-old female with VVC by KOH smear and culture treated with MONISTAT®7 Vaginal Cream. On Study Day 2 she noted a "red rash all over her body with itching." Her study medication was discontinued on day 3 and she was started of oral Benadryl® for 48 hours. The rash and pruritus resolved on Study Day 4. She went on to develop swelling of her arms and legs on Study Day 10 that was treated with hydrochlorothiazide and resolved on Study Day 11.

The Applicant's tabulation of severity of adverse experiences (AEs) by treatment arm is shown in Table 37.

Table 37. Severity of Adverse Experiences

Severity	Treatment Group			
	MCN (1200 mg) Vaginal [REDACTED] (N = 264)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 233*)	
	n	%	n	%
Mild	105	39.8	94	40.3
Moderate	100	37.9	92	39.5
Severe	56	21.2	47	20.2
Serious	3 ^a	1.1	0	0.0

* Severity not given for 1 of 234 adverse experiences reported.
^a=Adverse experience severities were classified as serious.

(Applicant's Table XIV, from Vol. 1.9, p. 08-000216)

The Applicant performed a Chi-square test on the distribution of AEs and found no statistically significant difference between the treatment groups ($p = 0.42$).

MO Comment: The three serious adverse experiences in the 1200 mg [REDACTED] group noted in Table 37 were the facial swelling and labial swelling noted above in patient number 00405 and the unsuccessful suicide attempt noted above in patient 01015.

MO Comment: The adverse experience for which a severity was not provided was vaginal pressure. The effect was classified as unlikely related to the study medication (MONISTAT[®]7), required no intervention or action, and resolved within 7 days.

MO Comment: Review of the serious AEs reveals two predominant categories of AEs. Those involving the genital/reproductive system and those not involving the genital/reproductive system. The non-genital reproductive system AEs are largely infrequently occurring events almost all of which had resolved by the end of study. Headache had the highest overall prevalence of non-genital/reproductive AEs with 6 severe headaches in the 1200 mg [redacted] group and 3 severe headaches in the MONISTAT[®]7 group (1 headache in each group was classified as a migraine headache). The rates for severe genital/reproductive AEs, which are predominantly local vulvar or vaginal symptoms, are comparable.

The Applicant tabulated the relationship of adverse experiences to study medication (Table 38).

Table 38. Relationship of Adverse Experiences to Study Medication

Relationship	Treatment Group			
	MCN (1200 mg) Vaginal [redacted] (N = 264)		MONISTAT [®] 7 (2% MCN) Vaginal Cream (N = 234)	
	n	%	n	%
Not related	138	52.3	138	59.0
Unlikely related	39	14.8	30	12.8
Possibly related	64	24.2	50	21.4
Probably related	15	5.7	11	4.7
Highly probably related	8	3.0	5	2.1

(Applicant's Table XV from Vol. 1.9, p. 08-000216)

MO Comment: The proportion of patients experiencing adverse events stratified by relationship to medication is comparable for each of the two study arms.

The Applicant noted that there were no findings on follow-up examination that demonstrated drug toxicity. The Applicant does note that one patient (Pt. Number 0714) in the 1200 mg [redacted] group had a large amount of the residue from the [redacted] still present in the vagina at the RV1 examination.

MO Comment: At Return Visit 2, Pt. Number 0714 did not have any abnormal findings on gynecologic examination. There are no reported adverse experiences associated with the persistence of the ovule material in this patient.

MO Comment: The comments transcribed from the CRFs were reviewed to see if there was any indication of problems related to the use of the ovule dosage form. No problems were apparent from review of the comments.

APPEARS THIS WAY ON ORIGINAL

Reviewer's Comments/Conclusions for Study 96-002

The study methods utilized allowed for the enrollment of two comparable populations for study. The efficacy results show MONISTAT[®] DUAL-PAK[®] to be similar to MONISTAT[®] 7 with regards to clinical, microbiological, and therapeutic response at both Return Visit 1 (RV1) and overall in the Applicant's evaluable for efficacy population. A modified intent-to-treat analysis performed by the Agency's Statistician found the MONISTAT[®] DUAL-PAK[®] similar to MONISTAT[®] 7 with regards to overall clinical, microbiological, and therapeutic response. An analysis of efficacy in the subset of evaluable patients compliant with the protocol specified visit windows found MONISTAT[®] DUAL-PAK[®] and its comparator statistically similar with regards to clinical, microbiological, and therapeutic response at RV1 and overall. The results of these three analyses of the study data support the therapeutic similarity of MONISTAT[®] DUAL-PAK[®] to its comparator, MONISTAT[®] 7 Vaginal Cream. In addition, recurrence rates for patients cured at RV1 were comparable between the two treatment groups.

Review of the safety data finds similar rates and distribution of adverse events across the two studies. The minor variations in rates that are observed involve small numbers of patients such that the rates are not significantly different. The number of patients discontinued from the study because of an adverse event is similar in number and nature across the study arms.

Overall the study supports the statistical similarity of safety and efficacy of the MONISTAT[®] DUAL-PAK[®] to its comparator, MONISTAT[®] 7.

APPEARS THIS WAY ON ORIGINAL