CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation
CLINICAL STUDIES

NDA:	204820
Name of drug:	Colchicine Capsules, 0.6 mg
Indication:	Prophylaxis of gout flares
Applicant:	West-Ward Pharmaceutical Corp.
Date(s):	Receipt: October 5, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
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Keywords:	NDA review

1 BACKGROUND

West-Ward Pharmaceutical Corp. is submitting a 505(b)(2) original new drug application for Colchicine Capsules, 0.6 mg for the prophylaxis of gout flares. The applicant proposes to rely on published literature and a bioequivalence study (Study number AA71527) for the proposed indication of prophylaxis of gout flares. West-Ward marketed Colchicine Tablets, 0.6 mg for over 25 years. According to West-Ward, the new capsule dosage form (b) (4) .

2 REVIEW

Gout is a painful and potentially disabling form of arthritis. Symptoms usually consist of intense episodes of painful swelling in single joints most often in the feet especially the big toe. These episodes are called flares.

The applicant has identified a bioequivalence study (Study CLI-P1-680) to establish the bioequivalence of colchicine to colchicine and probenecid, as well as, two published academic studies that demonstrate the effectiveness of colchicine for the prevention of gout flares, five open-label studies that contribute supportive data and one retrospective study evaluating colchicine. The clinical efficacy of colchicine is based solely on the published literature, which will be the focus of my review.

2.1 PAULUS ET AL., 1974

Fifty-one male patients with gout were randomized to colchicine plus probenecid group or probenecid plus placebo group in a randomized, placebo-controlled, double-blind, parallel group study. This six month study was conducted in two sites located in Los Angeles (LA), CA and Kansas City, KS.

> Inclusion criteria required a sUA > 7.5 mg/100 ml and a history of typical attacks of gouty arthritis that had responded to colchicine previously. Of the 51 subjects, 18 had crystal-proven gout and 13 had tophaceous gout. Subjects were excluded with renal disease associated with a cretonnes > 1.2 mg/100 ml.
>
> The study designs in LA and Kansas City were slightly different: in LA urate lowering agents were withdrawn two weeks before treatment began; in Kansas City, subjects received probenecid for two weeks before treatment. Patients were given identical-appearing tablets containing either 500 mg of probenecid or 500 mg of probenecid with 0.5 mg of colchicine and instructed to take one tablet three times a day. Patients were instructed to record any attacks and discuss them with the investigators at monthly visits. Investigators then rated attacks as mild, moderate or severe depending upon patients' description. Only attacks judged by the investigators to be moderate or severe were incorporated in the analysis. Acute gouty attacks observed by the investigators were judged on the observed temperature of the involved joint, tenderness, swelling of the joint

in centimeters compared to the contralateral joint, and area of redness. Nineteen of the 58 attacks reported were actually observed by the investigators. The primary endpoint was the number of attacks of gout per month of therapy for each patient. Only patients who clearly showed and maintained reduction in serum uric acid were included in the statistical analysis and are reported in the results.

Table 1 was duplicated from the publication. There were no reported differences in baseline characteristics.

Table 1. Characteristics of Subjects

	Colchicine-Probenecid	Placebo-Probenecid
Number enrolled	29	23
Number analyzed	20	18
Age (years) mean*	53	52
range	34-77	43-73
Number with Tophi*	3	4
Number with crystals in synovial fluid*	6	7
Duration of gout (years) (mean ± SE)*	10.5 ± 2.3	10.5 ± 1.8
Attacks of acute gout during 12 months prior to study (by history) mean ± SE*	4.2 ± 1.1†	3.2 ± 0.4
Number treated with uric acid lowering drug for at least 12 months prior to study*	12	12
Months of therapy*	109	94
Serum urate (mg/100 ml ± SE) before study*	8.4 ± 0.4†	9.2 ± 0.6

*Data for patients included in the analysis
†$P > 0.2$ (no significant difference)

Source: Table 1 from Paulus, et al., 1974

Table 2 from the article summarizes the effects of the serum urate levels before and after the study, the mean number of attacks of gouty arthritis per patient per month, and the number of patients with adverse events for each treatment group. Thirty-eight subjects were included in the analyses. The authors indicated that serum urate levels before and after were statistically different within each group. The relevance of this comparison is questionable since the analysis only included patients that showed and maintained a lowered serum urate level. Regardless, on average, for patients that maintained a reduced serum urate level, there were 0.48 flares per patient per month in the placebo-probenecid group and 0.19 flares per patient per month in the colchicine-probenecid group. In the table, the authors included two asterisks, one for each treatment group of the mean number of attacks per patient per month. I assume the authors' intent was to show that the rate of gout attacks in the colchicine-probenecid group was less than the rate of attacks in the placebo-probenecid group. As expected, there were more adverse events reported in the colchicine-probenecid group than in the placebo-probenecid group (15/20 versus 8/18, respectively); however, there was no significant difference between the two groups using a chi-square test. Table 2 was duplicated from the publication.

Table 2. Effects of Therapy

Treatment Group	Serum Urate mg/100 ml ± SE		Attacks of Gouty Arthritis per Patient per Month ± SE	No. of Patients with (Drug-related) Side Effects
	Before	After		
Colchicine-Probenecid	8.4 ± 0.4	6.3 ± 0.4†	0.19 ± 0.05*	15
Placebo-Probenecid	9.2 ± 0.6	6.2 ± 0.4†	0.48 ± 0.12*	8‡

*$P < 0.05$
†$P < 0.01$
‡$0.1 > P > 0.05$ (chi square analysis)

Source: Table 2 from Paulus, et al., 1974

The authors of this study concluded

> That treatment with 1.5 mg of colchicine, divided into 0.5 mg 3 times daily decreases the frequency of attacks of acute gout in subjects whose hyperuricemia has been satisfactorily controlled by probenecid.
>
> Due to the fairly common occurrence of side effects attributable to colchicine, and its failure to prevent all attacks of gout completely, indicate the need to exercise some clinical judgment in deciding which patients to treat with daily prophylactic colchicine and what dose to use.

The following were concerns identified in this publication.

1. I had concerns regarding the difference of the study design in the Kansas City versus Los Angeles sites. In the Los Angeles site, all the urate lowering drugs were removed two weeks prior to starting the study. However, in the Kansas City site, the patients were stabilized on probenecid prior to colchicine therapy. Since data has not been provided, I was not able to examine the possible effect of this variation.

2. Investigator rated the flares depending upon patients' description of flares and only attacks judged to be moderate or severe were included in the analysis. This could suggest that there are discrepancies in the patient reported flares versus the investigator observed flares. The impact of this on the analysis could not be determined.

3. Further, the authors included only patients that showed and maintained a lowering of serum urate levels in the analysis of the primary endpoint. The authors did not specify the criteria used to classify a reduction in serum urate levels. Also, since no data has been provided on the excluded patients, it is not clear how the results would have been impacted by an intent-to-treat analysis.

4. A Student's t-test is an appropriate method to compare the means of two groups. I assume that the overall mean attack of gout flares was calculated from the mean number of flares per patient. The basis for my assumption was the author's statement that the results were calculated from the number of attacks of gout per month of therapy for each patient. However, without the data, I could not verify the accuracy of my assumption. In addition, it was not clear if the authors' analysis accounted for patients that did not complete the study nor was the cause of withdrawal explained for every patient that withdrew.

2.2 BORSTAD ET AL., 2004

This is a randomized, placebo-controlled trial to evaluate the efficacy of colchicine in patients with chronic gouty arthritis.

> All patients were started on allopurinol 100 mg for crystal-proven chronic gouty arthritis. Their serum urate levels were monitored. The dose of allopurinol was increased in 100 mg increments until a serum urate level of less than 6.5 mg/dL was attained. Patients were then randomized to receive either colchicine 0.6 mg or placebo orally twice daily. The colchicine tablets and the placebo tablets were not identical in form and methods of treatment compliance were not obtained. Once daily dosing was utilized for subjects with chronic renal insufficiency. Subjects were evaluated at three and six months for evidence of acute gout flares and any clinical evidence of medication toxicity. Patients were to record length of flares, medications used, and overall assessment of the severity of flares on a visual analog scale (VAS).

The statistical analysis will use the intent-to-treat population defined as patients who were randomized and received a study drug. To evaluate efficacy,

> Average serum urate levels were compared between the two treatment groups at baseline, 3 months, and 6 months. A repeated measures analysis of variance statistic was used to compare the change of serum urate levels between the 0 and 3 month timepoints. This method was repeated for only those patients who experienced acute flares of gout. The treatment groups were analyzed at the 3 and 6 month timepoints regarding mean number of flares (T-test for equality of means), number of patients with > 0 flares (Pearson chi-square test), and number of patients with > 1 flare (Pearson chi-square test). Mann-Whitney analysis for nonparametric data was used to analyze mean VAS scores per flare and average length of flares in days between both groups, because the data were not normally distributed.

Out of the 51 patients enrolled in the study, 43 patients received treatment; 21 in the colchicine group and 22 in the placebo group. Table 1 summarizes the baseline demographics between the two groups. Table 1 was duplicated from the publication.

Table 1. Baseline demographics and clinical characteristics (n = 43: colchicine = 21, placebo = 22).

Demographic/Characteristic	Colchicine	Placebo	p
Mean age, yrs	63.5	62.5	0.798
Male, %	81	91	0.412
Caucasian race, %	67	73	0.665
Chronic renal insufficiency, %	14	9	0.664
Hypertension, %	90	77	0.412
Hypothyroidism, %	0.05	0.05	1.000
Coronary artery disease, %	29	27	1.000
Tophi, %	62	64	0.907
Alcohol use, %	33	18	0.255
Drugs affecting serum urate levels, %	38	55	0.364
Diuretic use at baseline, %	57	27	0.047
Flares during prior year (mean number)	2.48	2.09	0.343

Source: Table 1 from Borstad, et al., 2004

The authors of the Borstad et al. article state that

> There were a total of 77 acute gout flares: 12 in the colchicine group and 65 in the placebo group. Acute gout flares occurred in 33% of the colchicine patents and 77% of the placebo patients. Multiple gout flares occurred in 14% of the colchicine patients and 63% of the placebo patients. See Figure 1 (duplicated from the publication).

There were more cases of adverse events (diarrhea) in the colchicine group versus the placebo group, 38% and 5%, respectively.

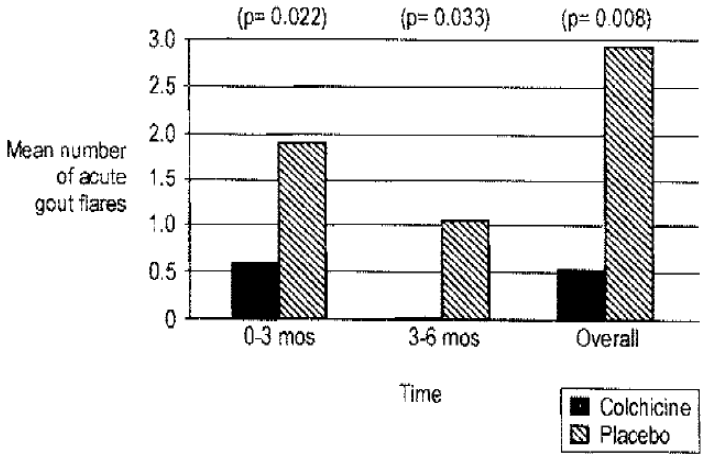

Figure 1. Mean number of acute gout flares at the 0–3 and 3–6 month time periods, and overall (n = 43: colchicine = 21, placebo = 22).

Source: Figure 1 from Borstad, et al., 2004

Thus, the authors conclude that colchicine decreases the average number of acute gout flares, decreases the likelihood of having one or multiple acute flares, and decreases the

severity of flares. Even though patients were only required to have three months of treatment, the authors suggest that there was a benefit for those patients who continued on the colchicine treatment for six months.

The following were concerns identified in this publication.

1. Blinding may have been compromised as the colchicine tablets and the placebo tablets did not have the same look. An awareness of treatment assignment could introduce observer bias and possibly result in an inflated treatment effect.

2. The t-test is an appropriate statistical procedure for comparing group means; however, it was unclear if this analysis accounted for patients having multiple flares. In addition, the authors provided a table that specified that 14% of patients withdrew in the colchicine group compared to 18% in the placebo group. However, it was unclear if the author's analysis between the two groups accounted for this patient withdrawal.

3 CONCLUSION

In conclusion, while the results from both studies seem to indicate that prophylactic use of colchicine in combination with a serum urate lowering drug reduces the occurrence of acute gout flares, I am unable to confirm the Authors' conclusions. There were shortcomings in the studies which raised concerns regarding the design, conduct, and statistical analyses of the data. Further, these studies appear to have been conducted for research purposes and were not subject to the rigor required for confirmatory studies submitted for regulatory review. With inclusion of the data and/or more details regarding the analysis, my concerns may have been alleviated. However because of the lack of needed information, I am unable to conclude that the articles have provided sufficient statistical evidence of efficacy.

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/s/

KIYA HAMILTON
04/05/2013

JOAN K BUENCONSEJO
04/05/2013
I concur.