

March 31, 2011

Division of Dockets Management, Docket No. FDA-2010-P-0614
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

We, the below signed FMF patients, are submitting this letter in response to the “Citizen Petition” filed by Mutual Pharmaceutical Company (Mutual) November, 26, 2010 which urges the FDA to delay approval of an NDA for colchicine submitted by a competitor. Mutual requests the FDA’s assistance in extending its proprietary reach by keeping its only potential competitor off the market for as long as possible.

This response is on behalf of patients with Familial Mediterranean Fever (FMF), a genetic condition for which colchicine is prescribed, and a condition which we (those signing this letter) have. In the U.S. FMF is much less common than gout, for which colchicine is also prescribed. It is imperative to understand that colchicine plays a very different role in the treatment of FMF than of gout. For FMF patients colchicine is not just one treatment option among others. **Colchicine is the only drug** that specifically treats the full range of FMF symptoms. It is so specific to FMF that response to it is the only diagnostic criterion common to all FMF patients. Colchicine is a **life-saving** drug for FMF patients; it prevents amyloidosis, a deadly complication of FMF. Thousands of FMF patients’ lives worldwide have been saved since its use for treating FMF was introduced in the 1970s. Colchicine also suppresses the painful and disabling inflammatory episodes of FMF and often **restores FMF patients’ lives to normal**. There is no cure for FMF. **We must take colchicine every day for the rest of our lives**. Our lives and our health revolve around colchicine, and there is no alternative to it. That is why any **disruption of our colchicine supply is a critical matter for us**.

Although the consequences of banning 4 brands of colchicine from the U.S. market are far more onerous for FMF patients than for gout patients, no FMF patients were included in the colchicine trial required for approval. There was no input solicited from FMF patients to determine the impact of designating colchicine as an orphan drug for the treatment of FMF. This designation granted Mutual four additional years of market exclusivity for the treatment of FMF, beyond the three granted for the treatment of gout. The consequence is that a widely available, inexpensive, life-saving drug is now less available and 50 times more costly for FMF patients, which is in contradiction to the spirit and the intent of the Orphan Drug Act.

FMF patients oppose any FDA action which would delay or otherwise preclude competing brands of colchicine from regaining entry into the U.S. market.

Our reasons for this position are medical. By excluding FMF patients from the colchicine approval process the FDA and Mutual ignored a fundamental and unusual clinical characteristic of FMF patients. We are, clinically speaking, a heterogeneous group. Our response to different brands of colchicine varies widely and is idiosyncratic – that is, one FMF patient may respond very well to brand A yet find brand B intolerable. Another FMF patient may have the exact opposite response to the same brands. There is no brand of colchicine that all FMF patients respond uniformly well to – or uniformly poorly to. Finding the best clinical response requires some trial and error, if the first brand prescribed does not provide optimal symptom control or has intolerable side effects. Our clinical heterogeneity is at the heart of our problems caused by the FDA when it removed 4 brands of colchicine from the market and replaced them with one.

Survey of FMF patients – a summary

To clarify this issue, FMF patients participating in two FMF support groups, responded to a survey asking about their experiences with and clinical reactions to various brands of colchicine. A more thorough brand analysis is attached to this letter. The following is a summary of results. Among the responses received, we included 23 respondents who named at least one brand of colchicine on the U.S. market. All brands named by the 23 respondents (whether US or foreign brands) were included in the analysis.

Summary of FMF Patients Responses to Various Brands of Colchicine

BRAND	Best Brand Ever	Worst Brand Ever	Satisfactory kept taking	Unsatisfactory kept taking	Unsatisfactory discontinued	Reactions reported
Colcrys	0	3/6 (50%)	1/6 (17%)	2/6 (33%)	3/6 (50%)	1,2,4,4,5,6,7,7
West-Ward	15/20(75%)	4/20(20%)	15/20 (75%)	5/20 (25%)	0	1,1,2,2,2,3,3
Watson	4/7 (57%)	2/7 (29%)	5/7 (71%)	0	2/7 (29%)	1,2,8
Odan	2/5 (40%)	0	4/5 (80%)	1/5 (20%)	0	-
Excellium	0	1/5 (20%)	1/5 (20%)	0	4/5 (80%)	1,1,1,1
Israeli	0	0	2/3 (66%)	0	1/3 (33%)	9
Qualitest	0	0	½ (50%)	0	½(50%)	10
Vision	0	0	0	0	1/1 (100%)	-

Reactions: 1= inadequate symptom control; 2= increased episodes; 3= needed increased dose 4=nausea; 5= stomach pain; 6= fatigue; 7= joint pain; 8= intestinal side effects; 9= abnormal liver function; 10=allergic reaction

Conclusions: These results demonstrate FMF patients' variable and idiosyncratic responses to different brands of colchicine. Twenty-three patients had tried 8 different brands of colchicine. Eight patients had tried only 1 brand, found it "satisfactory" and stayed with it. Fifteen patients tried an average of 3 brands each to find a "satisfactory brand." There was no brand of colchicine that uniformly provided satisfactory symptom control without side effects. The highest rated brand (West-Ward) with 75% "best brand" ranking and 75% "satisfactory" rating of symptom control still did not provide satisfactory results for 25% of patients. Those 25% achieved a satisfactory result with Watson (4 patients) and Odan (1 patient). Of note was the finding that 22/23 patients (96%) by trial and error found a "satisfactory" brand of colchicine. Also of note was that among 22 patients who had found a satisfactory brand, in only 1 case (5%) was Colcrys named as the satisfactory brand. All other brands named by FMF patients as achieving a "satisfactory" response have been banned by the FDA (or are from foreign sources). These results also suggest that permitting West-Ward back on the U.S. market as an approved drug will make a significant contribution to narrowing the therapeutic gap for FMF patients left by the sole brand, Colcrys. But even 2 brands are not enough to fill the variable needs of FMF patients, who continue to share contact information and instructions for acquiring their colchicine from foreign sources.

We request a response from the FDA to the following questions:

1. For physicians whose FMF patients have adverse clinical responses to Colcris, what does the FDA accept as therapeutic alternatives?
2. In what way do proprietary rights for the sale of colchicine in the U.S. serve the therapeutic needs of FMF patients?

In conclusion, we (FMF patients) in response to the November 26, 2010 petition of Mutual Pharmaceutical Company, oppose any FDA action that would further extend the proprietary rights of FDA-approved Colcris. We support all measures that would restore competing brands of colchicine to the U.S. market.

VERIFICATION

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about 2009 and 2010. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Not applicable I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this document.

Sincerely,



Janine Jagger, M.P.H., Ph.D., FMF patient (contact: jjc@virginia.edu)
Professor of Medicine
University of Virginia

With permission:
Jan Mcgonagle, M.D., FAAP, FMF patient

With permission:
Nancy Sparks Morrison, BS, MALS; FMF patient (nmorri3924@aol.com)

Moderator, FMF support group at yahoogroups.com; Moderator Eurodis English version, Rare Diseases Community

Survey Report: Comparative Colchicine Brand Response in FMF Patients

Janine Jagger, M.P.H., Ph.D., Submitted to FDA docket 3/31/11

This survey provides FMF patients' assessment of the quality of symptomatic relief from different brands of colchicine. The FDA required no inclusion of FMF patients in its approval protocol for NDA submissions of colchicine. Gout patients, the only patient group studied, are not a clinically relevant proxy for FMF patients. FMF patients in this survey report their experiences with several brands of colchicine, including the FDA approved brand, Colcrys. By extension, the impact on symptom control and quality of life of FMF patients consequent to the banning of all other brands of colchicine than Colcrys can be inferred.

The survey was designed and conducted by Janine Jagger, M.P.H., Ph.D., epidemiologist, academic researcher, FMF patient, and distributed to two online FMF patient support groups. Of 31 patients responding (from various countries), 23 were selected who took at least one brand of colchicine that is or was on the US market.

The **brand analysis** begins with FMF patients' experience with Colcrys, the sole brand now allowed for sale in the US by the FDA. It is followed by FMF patients' experiences with the West-Ward brand – the only other brand of colchicine applying to the FDA for reentrance into the US market as an approved drug.

Colcrys

Six out of 23 FMF patients (26%) reported ever taking Colcrys; 1/6 patients (17%) had a satisfactory response to Colcrys and continued taking it; 2/6 patients (33%) had an unsatisfactory response to Colcrys but continued taking it; 3/6 patients (50%) had an unsatisfactory response to Colcrys and discontinued taking it. 3/6 patients (50%) who took Colcrys listed Colcrys as the "worst brand" they had ever taken. 1/6 patients (17%) taking Colcrys listed Watson as the "worst brand" they had ever taken. 5/6 patients (83%) who took Colcrys listed West-Ward as the "best brand" they had ever taken. The verbatim comments of those reporting an unsatisfactory response to Colcrys (5 out of 6 patients) follow:

#1: Best brand: West-Ward / Worst brand: Watson

Colcrys: discontinued because of unsatisfactory response. Did not relieve my symptoms as well as West-Ward.

#2: Best brand: West-Ward / Worst brand: Colcrys (Odan also taken with unsatisfactory response)

Colcrys: I had to discontinue it because of an unsatisfactory response. Continuous cramps and stomach pain. It escalated in severity until I had to stop taking it. Also, nausea and ill feeling.

Odan: I'm taking it now because Colcrys was far worse. Stomach problems aren't as severe as Colcrys.

#3: Best brand: West-Ward / Worst brand: Colcrys (Odan also taken and satisfactory response reported)

Colcrys: I had to discontinue it because of an unsatisfactory response. Colcrys was not as effective. I started to have attacks again. I felt nauseous taking the drug.

#4: Best brand: West-Ward / Worst brand: Colcrys

Colcrys: I had an unsatisfactory response but I kept taking it. I had worsening joint problems, severe fatigue.

#5: Best brand: West-Ward / Worst brand: Colcrys
Colcrys: Unsatisfactory response reported but kept taking it. The fever and joint pain seem to come back sooner with Colcrys. We keep taking it because we have no choice. It is the only one available at the pharmacy here in AZ.

West-Ward

Twenty out of 23 FMF patients (87%) reported ever taking West-Ward; 15/20 patients (75%) had a satisfactory response to West-Ward and continued taking it; 5/20 patients (25%) had an unsatisfactory response to West-Ward but continued taking it; no patients discontinued West-Ward. 15/20 patients (75%) taking West-Ward listed it as the “best brand” they had ever taken. 4/20 patients (20%) who took West-Ward listed West-Ward as the “worst brand” they had ever taken; of those, 3 listed Watson and 1 listed Odan as their “best brands.” The comments of those reporting an unsatisfactory response to West-Ward (5 out of 20 patients) follow:

#1 Best brand: Watson / Worst brand: West-Ward

West-Ward: Unsatisfactory response reported but kept taking it. I have had more episodes of FMF while on it.

#2 Best brand: Watson / Worst brand: West-Ward

West-Ward: Unsatisfactory response reported but kept taking it. I had 1 attack per year with Watson or even less. Once i got to 18 months without an attack. I have been with West-Ward for more than a year now and I have had my 5th attack in around 14 months.

#3 Best brand: Watson / --

West-Ward: Unsatisfactory response reported but kept taking it. I had to take more of it to get the same response as Watson.

#4 Best brand: Odan / Worst brand: West-Ward

West-Ward: Unsatisfactory response but kept taking it. It didn't appear to protect me as well as Odan does.

#5 Best brand: Watson / Worst brand: West-Ward

West-Ward: Unsatisfactory response reported but kept taking it. My symptoms increased in frequency and strength. It was the only colchicine available at the time.

Watson

Seven out of 23 FMF patients (30%) reported ever taking Watson; 5/7 patients (71%) had a satisfactory response to Watson and continued taking it; 2/7 patients (29%) had an unsatisfactory response to Watson and discontinued taking it. 4/7 patients (57%) listed Watson as the “best brand” they had ever taken. 2/7 patients (29%) who took Watson listed Watson as the “worst brand” they had ever taken; of those, both listed West-Ward as their “best brand.” The unsatisfactory response to Watson (2 out of 7 patients):

#1 Best brand West-Ward/ Worst brand Watson. Discontinued use because of an unsatisfactory response. My symptoms did not go away and when I increased the dose it caused intestinal side effects

#2 Best brand West-Ward/ Worst brand Watson. Discontinued use because of an unsatisfactory response. Attacks became worse. The medication was ineffective.

Odan

Five out of 23 FMF patients (22%) reported ever taking Odan, a Canadian brand. They are included here because respondents taking Odan had also taken a brand on the US market. 4/5 patients (80%) had a satisfactory response and 1/5 patients (20%) had an unsatisfactory response but continued taking it. Odan was listed as the “best brand” ever taken by 2/5 patients. The unsatisfactory response of one patient:

#1 Odan: I'm taking it now because Colcrys was far worse. Stomach problems aren't as severe as Colcrys.

The remaining four brands mentioned were:

Excellium: Taken by 5 respondents. One respondent had a satisfactory response and the remaining 4 discontinued this brand because it did not reduce their FMF symptoms. The 4 respondents “best brands” were 2 West-Ward, 2 Watson.

Israeli colchicine: Taken by 3 respondents. Two respondents has a satisfactory response and the third discontinued use because of abnormal liver function tests (the cause of which was not determined). This patient’s “best brand” was West-Ward.

Qualitest: Taken by 2 respondents. One respondent had a satisfactory response and the other discontinued use because of an apparent allergic reaction. This patient’s “best brand” was Watson.

Vision: Taken by 1 respondent and discontinued for an undisclosed reason. The respondent’s “best brand” was Watson.

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