

Clinical and Clinical Pharmacology Review

Date	October 22, 2011
From	Sarah Yim, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	(b) (4)
Supplement#	
Applicant	Mutual Pharmaceutical Company/URL Inc.
Date of Submission	April 29, 2011
PDUFA Goal Date	previously October 29, 2011, (b) (4)
Proprietary Name / Established (USAN) names	Colcrys/colchicine
Dosage forms / Strength	Granules in capsule/0.3 mg
Proposed Indication(s)	1. Familial Mediterranean Fever (FMF)
Recommended:	<i>No action,</i> (b) (4)

1. Background

(b) (4)

The NDA contained an interim study report of Study MPC-006-09-1001, a pharmacokinetic (PK) and safety study of a Colcrys granule formulation in pediatric patients with Familial Mediterranean Fever (FMF), conducted to meet the terms of a pediatric written request for colchicine.

The original approval of Colcrys (tablet formulation) for FMF on July 29, 2009, resided with NDA 022352. Colcrys® (colchicine) was approved for FMF in adults and children 4 years of age and older based upon publications of three randomized double-blind, placebo controlled, crossover studies involving oral colchicine as prophylaxis of acute attacks of FMF. The pediatric study requirement under the Pediatric Research Equity Act was waived due to FMF's orphan designation.

On March 30, 2010, a pediatric written request (PWR) was issued for a study to investigate the PK and safety of colchicine in pediatric patients aged 2 to 4 years and above (since PK was not available in any age group). This request specified 10 patients in each of the following age categories: 2 to < 4 years, 4 to < 6 years, 6 to < 12 years, 12 to < 16 years, and 16 to < 65 years. A response was required on or before October 30, 2011.

On December 22, 2010, Mutual/URL submitted a request to amend the PWR to reduce the required number of patients in each age group to the numbers they currently had enrolled in Study MPC-006-09-1001 (5 patients 2 to < 4 years, 3 patients 4 to < 6 years, 6 patients 6 to < 12 years, and 6 patients 12 to < 16 years of age). The PWR amendment request was discussed with the Pediatric Review Committee (PeRC) on April 13, 2011. PeRC concluded that the 10 patients per age category requirement for the PK portion of the study might be met as long as

“the final number of patients enrolled in each group will be determined based on obtaining mean apparent clearance and apparent volume of distribution with a standard error of 20% or less” because this was a requirement for an outcome rather than a specific number. And since determining the PK of colchicine involves a certain number of patients be enrolled, the PeRC did not feel that this applied to the number of patients to be studied for safety. In fact, PeRC also decided [REDACTED] (b) (4)

However, [REDACTED] (b) (4) was submitted on April 29, 2011, before an amended PWR could be sent. [REDACTED] (b) (4) the interim clinical study report should be considered as “fairly responding” to the PWR.

Subsequent to this submission, Mutual/URL requested a second amendment to the PWR on August 4, 2011, to reduce the numbers in each age group to match available data. In addition, because of a data integrity issue pertaining to mislabeling of PK samples, data from only 8 adult patients ages 16 to < 65 years would be available for the population PK analysis, although data on a total of 18 adults could be used for a comparative safety assessment. To address this deficiency, Mutual/URL also notified the Agency of their plan to submit additional data as it became available, planned for the end of August and mid-October.

[REDACTED] (b) (4)

2. Results

[REDACTED] (b) (4) contained the reports of two studies—Study MPC-006-09-1002, a randomized, four-way crossover, open-label, single dose study conducted in 24 healthy adult volunteers, and Study MPC-006-09-1001, open-label, steady state PK, and 90-day safety study of Colcrys (colchicine, USP) Pediatric Granules, 0.3 mg in children 2 to 16 years of age and adults with FMF.

Study MPC-006-09-1002, Colcrys Granules Relative Bioavailability Study

In this study, subjects received a single oral 0.6-mg Colchicine dose of the following treatments with a washout period of 14 days between treatments. Treatments were as follows:

- A Colcrys Pediatric Granules in Simple Syrup (fasted)
- B Colcrys Pediatric Granules in Simple Syrup (fed)
- C Colcrys Pediatric Granules in Applesauce (fasted)
- D Colcrys Tablets (fasted)

The main comparison was Group C versus Group D for bioequivalence, with the comparison of Group A versus Group B for food effect. Results of this study showed that Colcrys Pediatric Granules were not bioequivalent to Colcrys tablets, and had less bioavailability and lower exposure per nominal dose. Furthermore, Colcrys granules (sprinkled in simple syrup) were associated with a relatively large food effect—food consumption decreased the

bioavailability of Colcrlys granules. Furthermore, food effect information obtained with granules sprinkled in applesauce (recommended dosing vehicle) is not available and, in light of the bioavailability differences between granules and tablets, it is not clear if the same food effect information obtained with simple syrup can be applied to applesauce. However, based on these data, Mutual/URL proposed taking the product on an empty stomach. In contrast, Colcrlys tablets did not exhibit a clinically significant food effect and recommended dosage and administration is irrespective of food consumption.

Study MPC-006-09-1001, PK and Safety Study of Colcrlys granules

This study is an open-label, parallel-group, multiple-dose PK and safety study of Colcrlys granules in pediatric and adult patients with FMF, intended to fulfill the terms of the PWR. The study consists of four phases: a screening period, a 7-day up-titration phase (if required), a fixed-dose 14-day phase with PK sampling on Days 14 and 15, and a flexible dose phase for continued safety assessment, for a total study duration of 90 days. A total of 10 patients were to be studied in each of the following age groups: 2 to < 4 years, 4 to < 6 years, 6 to < 12 years, 12 to < 16 years, and 16 to < 65 years.

(b) (4) was submitted on April 29, 2011, there were fewer than 10 patients in the 2 to < 4, 4 to < 6, and 12 to < 16 year age categories. There were 17 patients in the 16- to < 65-year age category, but a data integrity issue discovered after the April 29, 2011 submission reduced the number of patients to less than 10 that could provide reliable data for PK analyses.

(b) (4) data on at least 10 patients had been provided for each age category except the 4- to < 6-year olds and those 16 to < 65 years of age.

The data submitted appeared to meet PWR's PK goals of a standard error of 20% or less.

Preliminary evaluation of the available safety data submitted did not reveal any new safety signals. The most commonly reported AEs were those known to occur with colchicine or FMF itself. No consistent effects of colchicine on growth could be discerned in the pediatric data submitted.

3. Conclusions

The data in (b) (4) suggest that Colcrlys granules are not an age-appropriate formulation (b) (4) for the following reasons:

- Colcrlys granules are not bioequivalent to Colcrlys tablets (lower bioavailability), and would necessitate different dosing if used in the same age group (e.g., 4 to < 6 years of age, an age group for which Colcrlys tablets are already approved), raising concerns regarding the potential for medication/dosing errors. If used in other age groups at equivalent doses, efficacy may be compromised.
- Colcrlys granules have a food effect, whereas Colcrlys tablets do not. This would necessitate labeling distinct from currently approved Colcrlys tablets and raises concerns regarding the potential for medication/dosing errors.

- Due to its size, the Colcrys granules capsule container raises concerns regarding choking hazard if mistakenly swallowed.

Additionally, the required patient numbers in the PWR for safety were not met. The PWR specified at least 10 patients per age category, in the categories of 2 to < 4 years, 4 to < 6 years, 6 to < 12 years, 12 to < 16 years, for a total of at least 40 pediatric patients. At the time (b) (4) data was submitted on 10 patients 2 to < 4 years, 8 patients 4 to < 6 years, 17 patients 6 to < 12 years, 10 patients 12 to < 16 years, and 8 patients whose age was at least 16 years.

Preliminary review of the safety data submitted suggested the safety of the Colcrys granules was consistent with the known safety profile of colchicine. No consistent effects on growth could be discerned in the timeframe of the study (90 days).

(b) (4)