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2000 Lake Boulevard, NE
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Dear Dr. Cohen:

It has been brought to my attention that some members of ACR have been attempting to prevent FDA from removing illegal unapproved colchicine products from the market due to concerns for price-based patient access. While I appreciate the concerns that your members have for the welfare of their patients, I believe that these communications should have come to us first so that a lot of misinformation could have been avoided. We respect the ACR and we would have been responsive to a meeting or a letter expressing your concerns. I would like to take this opportunity to provide ACR with medical, scientific, industrial, regulatory, and legal aspects of colchicine that might be unfamiliar to your members. Lastly, through your recent meeting with our Chief Medical Officer Dr. Matt Davis, and our Executive Director of Clinical Development Dr. Suman Wason, we have received your input and expanded our Patient Assistance Program to assure that all needy patients are covered.

I. Avenues to Discuss Patient Assistance Programs

FDA is charged with assuring that pharmaceuticals for Americans are safe and effective. FDA requires companies to go through the drug application process, and have their chemistry and manufacturing testing methods, labeling, data, and clinical studies reviewed by FDA before distribution of medication to patients. After approval of a drug application, FDA enforces regulations on how changes can be made to manufacturing and testing processes and conducts field inspections to assure that the company is complying with the FDA-approved processes. FDA also monitors and controls changes through Annual Reports, Application Supplements, and other formal reporting mechanisms. All of these procedures occur for brand (New Drug Applications, called NDAs) and generic drugs (Abbreviated New Drug Applications, called ANDAs). None of this oversight occurs for unapproved products since there are no FDA-approved processes for the manufacturer to be held accountable to and there is no FDA-approved drug application for the required periodic reporting to, and review by, FDA.

However, FDA does not control the price of medications. I was informed about the ACR letter to FDA during an interview with a news reporter. We first received a copy of the ACR letter about two weeks thereafter when someone from our Company found it on the ACR website. I have also been told that our Chief Medical Officer had requested a meeting with ACR, which was communicated to ACR through two of its prominent members, in December 2009 but ACR did not wish to meet him at that time. Now that we have received input from you, and from the leading FMF group, we have used this input to expand our assistance programs and meet the needs of additional patients.

II. Regulatory, Scientific, and Legal Background That Many Physicians Don't Know

In 2006, FDA ratified its program to remove unapproved pharmaceuticals from the U.S. market to protect patients. This policy is called the Compliance Policy Guidance (CPG). According to the CPG, when a particular drug is needed to treat disease, FDA will generally wait until there is an FDA-approved version before removing the unapproved product from the market.

Colchicine is a medically necessary pharmaceutical in the treatment of various diseases but has only been available as an unapproved drug until the FDA approval of Colcrys®. Now that Colcrys® has been approved by FDA, and is available in sufficient quantities for all patient needs, some may still ask why FDA would remove unapproved colchicine and why such an action would be helpful to physicians and patients (beyond the fact that the unapproved products are illegal, FDA has a formal policy guidance on this, and manufacturers of the illegal product were given notice over two years ago).

Apparently, some physicians have called the illegal unapproved colchicine products "generic" including in public forums and letters to the FDA. Unapproved colchicine is neither legal nor generic.

Regarding the legal status of unapproved colchicine, please refer to the Warning Letter from FDA to Sunshine Pharmaceuticals to see that unapproved colchicine is illegal (http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm197966.htm see section titled "Misbranded and Unapproved New Drugs"). I think that those who advocate in favor of keeping "generic" colchicine on the market don't realize that they are really advocating giving an illegal, uncontrolled, pharmaceutical product to patients when an FDA-approved, legal, controlled colchicine is available. I don't think that physicians would want to be on this side of the issue if they realized the implications.

Regarding being a generic drug, versus an unapproved drug, the following is only a small sampling of what a generic drug must do to receive FDA-approval that an illegal, unapproved drug has not done.

A. Chemistry

There are impurities in all pharmaceutical products. Some of these impurities are known to have medical dangers associated with them and some are not yet fully characterized.

A generic drug has had its analytical (chemistry testing) methods reviewed by the FDA to assure that the methods do, in fact, give accurate test results for the amounts of impurities and active drug that are in a tablet. Testing methods can be inaccurate for many reasons including signals from the excipients that interfere with signals from the active ingredient or impurities, non-linearity at low concentrations, or unreliable reproducibility of the methods. That is why these methods undergo extensive validation that is reviewed and approved by FDA as part of the drug approval process. The illegal colchicine products have not undergone any such FDA review and approval (or rejection) process.

For example, in our FDA-approved NDA for Colcrys®, we have limits of N-deacetyl-N-formyl colchicine, 2-o-demethyl colchicine, and 3-o-demethyl colchicine of “not more than (NMT) 0.42%”. The MSDS (Medical Safety Data Sheet) of the first listed impurity states that it has a lower LD50 (lethal dose 50%) than colchicine. There are no FDA controls on impurity levels in illegal colchicine. Of note, there are no USP Monograph tests for these impurities either.

For all pharmaceuticals, it is widely known that impurities can vary depending upon the manufacturing source. For FDA-approved products, the sources of raw material are part of the FDA-approval process and there are regulations regarding the science required to get another raw material source approved by FDA including FDA inspection of the raw material manufacturing facilities. The illegal unapproved colchicine manufacturers have not committed themselves to any such regulations by skirting the FDA-approval process. With so many instances of contaminated products coming to US consumers from foreign countries, this is an unnecessary risk for patients who take colchicine since FDA-approved Colcrys(R) is now available. URL Pharma pays approximately three times the price of the raw material, that is used by manufacturers of illegal unapproved products, to get custom-made colchicine with substantially lower levels of impurities. This higher-purity material resulted from URL Pharma’s scientists working with the raw material suppliers to change their processes to eliminate much of the impurities. These suppliers did not produce such pure colchicine before we worked, and then contracted, with them.

Another example are the lumi-colchicine impurity levels. FDA asked us to commit to monitoring and limiting the lumi-colchicine impurities because the molecular structures contain features that indicate that they could be toxic. There is no indication from the scientific literature that their toxicity has been studied. The limit which FDA asked us to maintain is FDA’s standard limit based upon the total daily intake of an impurity that has

no toxicity information. URL Pharma manufactures Colcrys® using yellow lights in the manufacturing rooms as part of our FDA-approved processes to avoid the creation of lumi-colchicine impurities. No such legally-binding FDA commitments have been made by manufacturers of unapproved colchicine in the manufacturing processes or in their specifications for impurities.

Even if a physician thinks that he has prescribed illegal colchicine for years and observed no consequences from it, that physician simply can't know what impurities might have been in those batches, what the long term consequences are, nor what impurities may be present in the next batch of unapproved colchicine. Even if an illegal colchicine product was manufactured to USP standards, the USP does not have tests for colchicine impurities but our FDA-approved Colcrys® does. Until an FDA approved colchicine was available, this was a necessary risk, or trade-off, for the treatment of patients. But now that Colcrys® has been approved by FDA, I don't think that any physician would advocate for an uncontrolled illegal product after knowing this information.

These examples are only a small sampling of the chemistry controls that we have implemented for Colcrys®.

B. Manufacturing Controls

There are numerous manufacturing controls that are included in the FDA approval process for a "generic" drug. Illegal unapproved colchicines have not undergone this FDA review.

For example, there is a pharmaceutical concept called Content Uniformity. This means the assurance that every tablet has the correct amount of drug in it.

Content uniformity is particularly difficult to achieve when there is a low dosage drug like colchicine. The smallest tablet that someone can comfortably handle is about 80 to 100 mg. Colchicine tablets have less than 1 mg. of drug so the vast majority of the tablet is inactive ingredients. It is very easy for a large blender, of a million tablets, to produce "cold spots" where there is no drug and "hot spots" where there is too much drug. This results in some tablets having dosages that are too high or too low which, in the case of colchicine, could result in tablets with 100 times the drug that it should have or having no drug at all. The distribution of the drug uniformly in the blend of inactive ingredients involves the particle size of the drug, the particle size of the different inactive ingredients, mixing equipment configuration, speed, and time, and the sequence of additions and mixing of ingredients. Even over-mixing, after there is complete blend uniformity, can form static electrical charges on some particles causing them to agglomerate with the blend returning to an inhomogeneous state. And even after mixing and achieving full Blend Uniformity, there needs to be assurance that the tableting process produces tablets with consistent and acceptable Content Uniformity.

Quite simply, this is an area of intense sampling and testing to assure reproducibly achieving the needed tablet characteristics and is part of the FDA approval process. Generic and Branded drugs undergo this FDA review. Illegal, unapproved colchicine has not undergone this FDA review. Even if one found that some tablets of illegal colchicine were consistent, there would be no assurance that the next batch would meet these standards since they are unapproved.

C. Generic Equivalence to a Brand

The Brand company, in doing the research for an NDA application, must prove safety and efficacy to receive FDA approval. A "generic drug" must demonstrate that it meets FDA's chemistry and manufacturing standards, prove bioequivalence to the brand product, and copy the brand labeling especially in the area of safety. Illegal unapproved colchicine has not done any of this. It is factually incorrect, and can be misleading and dangerous to the public, to call illegal colchicine products "generic".

In the URL Pharma AGREE clinical study, we tested our formulation of Colcrys(R) with our dosing regimen of two tablets followed by one tablet one hour later compared to the currently common medical practice of 1 tablet per hour for 8 hours and to a placebo. The high-dose was associated with significantly more diarrhea, vomiting, and other AEs than low-dose or placebo. With high-dose, 40 (76.9%) had diarrhea [Odds Ratio 21.3, 95% CI 7.9 – 56.9], 10 (19.2%) severe diarrhea, and 9 (17.3%) vomiting. With our FDA approved low-dose, (23.0%) had diarrhea [Odds Ratio 1.9, 95% CI 0.8 – 4.8], 0 severe diarrhea, and 0 vomiting. In the published literature[1], 100% of patients had diarrhea[1].

The prescribing information for illegal unapproved colchicines recommend up to 16 tablets to treat a gout flare. How can they do this when our AGREE trial demonstrated full efficacy using the Colcrys® formulation and our three tablet dosing regimen while eliminating most adverse reactions? Because the illegal products are not generic so they do not copy the FDA approved Colcrys® label.

I have been told that ACR does not have a formal recommendation for the correct dosing of colchicine to treat a gout flare. I do know that many physicians, and patients, will refer to the package insert labels of illegal unapproved colchicine products for guidance and, if followed, then they will be exposed to potentially dangerous overdoses that are completely unnecessary since the FDA approval of Colcrys(R). I do not think that it is responsible for the illegal product to remain on the market.

[1] Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks PM, Jones M. Does colchicine work? The results of the first controlled study in acute gout. Aust N Z J Med. 1987 Jun;17(3):301-4.

D. Labeling

Another example of illegal colchicine not having "generic" drug labeling, representing a hazard to patients, is the case of drug-drug interactions (DDI). The illegal colchicines do not list any DDIs in their labels. URL Pharma's research found many DDIs that can raise colchicine blood levels by almost 300%. A physician, who suspects that his patient is suffering from a colchicine overdose due to a DDI, can look at the package labeling for an illegal colchicine and feel comfortable that no such DDI exists. It is a false comfort. FDA has reports of 169 deaths associated with illegal colchicine and at least 60 are suspected to be the result of DDIs. It is reasonable to expect that the number of reported deaths would be much higher if physicians knew that the drug label that they consulted, which shows no DDIs, is illegal and not FDA-approved. Calling these products "generic" means that their labels have been approved by FDA and that is clearly not the case here.

The FDA-approved Colcrys(R) label contains dose reduction guidance in the presence of DDIs. Unapproved colchicine labels do not have this information. Also, if there is a colchicine overdose, then the illegal colchicine labels report that recent evidence shows that dialysis can remove colchicine from the blood. Our research found that dialysis does not remove colchicine from the blood and the Colcrys® label properly informs physicians in this regard. In cases of colchicine overdose, physicians may try to remove colchicine from the blood, using dialysis, with the belief that the instructions on the package label were FDA-approved and thus correct. Calling illegal colchicine "generic" is a statement that the unapproved colchicine labeling is FDA-approved which is just not correct. Generics are legal. Unapproved drugs are not.

The manufacturers of unapproved colchicine were told publicly by FDA two years ago that they need to seek FDA approval or “colchicine tablets that are marketed without FDA approval could be subject to FDA enforcement at any time.” (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm119642.htm; Q&A number 6, second paragraph). In ClinicalTrials.gov, you will see that URL Pharma (or our subsidiary Mutual) conducted 17 clinical trials and the manufacturers of illegal colchicine did not conduct even 1.

III. Unnecessary Risks for Patients

Throughout my life, I have come to recognize that there is an enormous amount of knowledge in so many disciplines of which I was unaware. In my 21 years in the pharmaceutical industry, I have witnessed a dramatic advancement in the complexity and sophistication of pharmaceutical manufacturing and quality science, and the corresponding regulatory oversight and controls. As a physician, I was not taught any of this since it is in the realm of FDA, pharmaceutical science, and the pharmaceutical industry.

I truly believe that the ACR as an organization, and the individual members of ACR, are committed to improving the health, welfare, and benefit of their patients. I believe that those who have called the illegal colchicine "generic" were unaware of the implications of their statements. I would think that any reasonable physician who knows these facts would now recognize the value that URL Pharma has brought to patients, the necessity of the FDA's Compliance Policy Guidance program to remove unapproved drugs, and they would want to clarify the record. I assume that, after knowing the facts, physicians will want a safe and effective, vastly improved, legal, FDA-approved, widely available, product for their patients.

IV. Patient Access

But there is still the concern for the price of FDA-approved Colcrys(R) since people need to be able to access their medication.

Even though our Patient Assistance Program was already one of the most generous in the pharmaceutical industry, we have heard the concerns of the ACR and the FMF community and we have responded to them.

We have enhanced our Patient Assistance Program parameters and are working with the administering company to implement the following changes as soon as they are able to do so. Our improved Patient Assistance Program will cover patients up to 6 times the Federal Poverty Limit (FPL). We will update you when we have more visibility on the implementation date. But I want to assure you that we are working aggressively to get this expanded program into effect.

1. The previous Patient Assistance Program was only for people with annual incomes up to three times the Federal Poverty Limit which is $66,000 for a family of four. The program provided these patients with Colcrys® for $5 per month.

2. In response to the ACR and FMF communities, we are expanding our Patient Assistance Program for a family of four as follows:

    a. For an income up to $66,000 per year, the cost of a Colcrys® prescription will be $5 per month.

    b. For an annual income between $66,001 and $88,000 per year, the cost of a Colcrys® prescription will be $10 per month.

    c. For an annual income between $88,001 per year and $110,000 per year, the cost of a prescription of Colcrys® will be $20 per month.

d. For an annual income between $110,001 per year and $132,000 per year, the cost of Colcrys® will be $30 per month.

e. There is no time limit set for this program. I would note to you that we have only one other branded product, for which we received FDA-approval more than one year ago, and the Patient Assistance Program for that product has been in existence for 4 years with no changes made to it during those 4 years.

3. For patients with health insurance, our existing program reduces their co-pays from as high as $90 per prescription down to $25 per prescription. There is an expiration date on this program of August 2010 but we intend to continue the program thereafter.

Conclusion

In conclusion, I believe that physicians who are advocating that illegal unapproved colchicine remains on the market for their patients, with all of its hazards when an FDA-approved superior product is readily available, have done so with noble intentions but without a full appreciation of the facts. We have heard the financial concerns of the ACR, and the FMF community, and we have responded with a program that provides FDA-approved, legal, colchicine to everyone who needs it at minimal costs. I would hope that those who have been critical of FDA's and our attempts to bring a safe and effective colchicine to the market will give us some credit for what we have done for patients and the medical community. I also hope that these individuals, with this information, will make an effort to correct the public record on unapproved versus approved pharmaceutical products.

Yours Truly,

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