IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

TAKEDA PHARMACEUTICALS U.S.A., INC. 1 Takeda Parkway Deerfield, IL 60015, Plaintiff, v. SYLVIA MATHEWS BURWELL, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, 200 Independence Avenue, S.W. Washington, DC 20201, and MARGARET HAMBURG, M.D., in her official capacity as COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, 10903 New Hampshire Avenue, Silver Spring, MD 20993, Defendants.	Civil Action No. _____

VERIFIED COMPLAINT FOR DECLARATORY, INJUNCTIVE, AND OTHER RELIEF

Plaintiff Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") hereby brings this Verified Complaint against Defendants Sylvia Mathews Burwell, solely in her official capacity as Secretary of the Department of Health and Human Services ("HHS"), and Margaret Hamburg, M.D., solely in her official capacity as Commissioner of Food and Drugs, head of the Food and Drug Administration ("FDA" or the "agency"), and alleges as follows:

INTRODUCTION

1. This is an action to hold unlawful and set aside FDA's approval on September 26, 2014[1] of an application submitted by Hikma Pharmaceuticals LLC ("Hikma") under Section 505(b)(2) of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(b)(2), for permission to market Mitigare (colchicine) capsules, 0.6 mg ("Mitigare"), a single-ingredient colchicine product indicated for the prophylaxis of gout flares. FDA's approval of Mitigare was unlawful, arbitrary and capricious for no fewer than three separate reasons. *First*, FDA acted arbitrarily and capriciously in approving Hikma's Section 505(b)(2) application for Mitigare without requiring the label to contain critical safety information that FDA previously stated was necessary for single-ingredient oral colchicine products. *Second*, FDA's approval of Hikma's application for Mitigare was unlawful, arbitrary and capricious because, as approved, Mitigare is not safe in light of the defects in its label. And *third*, FDA's failure to require Hikma to reference Takeda's own colchicine drug, Colcrys®, in its application interfered with Takeda's rights to participate in the administrative process, including the Paragraph IV certification process under the Hatch-Waxman Act and the Citizen Petition process. As a result, FDA's decision is unlawful, arbitrary, capricious, an abuse of discretion, and otherwise violates the Administrative Procedure Act (the "APA").

2. FDA acted unlawfully, arbitrarily and capriciously by approving Hikma's Mitigare product without the critical safety information that FDA previously had expressly found to be necessary for single-ingredient oral colchicine products. FDA has clearly stated that the labeling for a

[1] Takeda became aware of the approval on September 30, 2014 from a Hikma press release of that date.

prophylaxis product must disclose the dosage for treatment of an acute gout flare due to the risk of cumulative toxicity. Ex. 1, Letter from J. Woodcock to G. Veron, FDA Docket No. FDA-2010-P-0614 (May 25, 2011) at 1. In contrast to FDA's explicit statement, the Mitigare label states simply that Mitigare has not been studied in acute gout flares. Ex. 2, Mitigare Label, at 1, 2. In addition, the Mitigare label does not include the specific dose adjustments to avoid potentially fatal drug-drug interactions. *See id.* Mitigare's label is in direct conflict with FDA's stated position on this very issue in an earlier Citizen Petition response. Ex. 1 at 19.

3. By permitting Hikma to avoid the specific drug-drug interaction dose adjustments and the low-dose regimen for gout flares, FDA allowed Hikma to proceed without referencing Colcrys® and without certifying to the Colcrys® patents. *See* 21 U.S.C. § 355(b)(2)(A). In so doing, FDA denied Takeda the opportunity to file patent infringement claims under Hatch-Waxman and invoke its right to a 30-month stay of Mitigare's approval. *See* 21 U.S.C. § 355(c)(3)(C). In addition, FDA denied Takeda the opportunity to file a Citizen Petition challenging Hikma's application on the merits. FDA also created significant safety risks to the patient public.

4. FDA's actions pose a substantial and imminent harm to prospective patients who will be placed on Mitigare. Before FDA approved Colcrys® and removed the unapproved products from the market, the unapproved products generally contained labeling information that lacked the very same safety information omitted from the Mitigare label recently approved by FDA. Labeled in this manner, the earlier products were associated with a significant number of fatalities related to drug-drug interactions and colchicine toxicity. FDA's actions will also irreparably harm Takeda. Instead of following its own previous proclamation about the necessity of including drug-drug interaction dosing adjustments and low-dosage regimen safety information, FDA instead left the Mitigare label devoid of

that information. This action dispensed with the need for Hikma to reference Colcrys® and certify to the patents listed for Colcrys®. Had Hikma certified to these patents, the patent certifications likely would have included a Paragraph IV certification, which in turn would have required Hikma to notify Takeda of the pending application. Such notice would have triggered patent litigation and consequently a statutorily mandated 30-month stay of Hikma's application. See FDCA §§ 505(c)(3); 505(j)(5)(B)(iii). Such notice also would have alerted Takeda to the pending application and permitted it the opportunity to file a Citizen Petition to contest FDA's approval of the drug. In short, absent immediate relief, the patient public and Takeda will suffer grave and irreparable harm.

PARTIES

5. Plaintiff Takeda Pharmaceuticals U.S.A., Inc. is a Delaware company with its principal place of business at 1 Takeda Parkway, Deerfield IL 60015. Takeda develops, acquires, markets, and sells pharmaceutical products for a wide range of conditions. Takeda holds an approved NDA for Colcrys®.

6. Defendant Sylvia Mathews Burwell is the Secretary of HHS and is responsible for administering and enforcing the Food, Drug, and Cosmetic Act, 21 U.S.C. § 321, et seq. Defendant Burwell is being sued in her official capacity only. Defendant Burwell maintains an office at 200 Independence Avenue, S.W., Washington, D.C. 20201.

7. Defendant Margaret Hamburg, M.D., is the Commissioner of Food and Drugs and is responsible for supervising the activities of FDA, an administrative agency within HHS. Defendant Hamburg is being sued in her official capacity only. Defendant Hamburg maintains offices at 10903 New Hampshire Avenue, Silver Spring, MD 20993.

JURISDICTION AND VENUE

8. Jurisdiction in this Court is grounded upon and proper under 28 U.S.C. § 1331 (federal question), in that this is a civil action arising under the laws of the United States; 28 U.S.C. § 1346, in that this case involves claims against the federal government; 5 U.S.C. § 702, in that Takeda is seeking judicial review of an agency action from which it has suffered a legal wrong, has been adversely affected, and has been aggrieved; 28 U.S.C. § 1361, in that this is an action to compel an officer of the United States to perform his duty; 28 U.S.C. §§ 2201-2202 (declaratory judgment), in that there exists between Takeda and the Defendants an actual, justiciable controversy as to which Takeda requires a declaration of its rights by this Court as well as preliminary and permanent injunctive relief to prohibit the Defendants from violating laws and regulations; and 21 U.S.C. § 355(q) and other sources of law, in that the conduct complained of constitutes final agency action.

9. Venue is proper in this Court under 28 U.S.C. § 1391(b) and (e) because this is a civil action in which the Defendants are officers of the United States acting in their official capacities and one of the Defendants maintains her office and conducts business in this judicial district. Moreover, a substantial part of the events giving rise to the claims herein occurred within this judicial district.

10. Takeda has standing to bring the present lawsuit because it is suffering and faces additional actual injury as a result of FDA's decisions and because it is within the zone of interest of the relevant statutory provisions.

NATURE OF THE CASE

I. Statutory and Regulatory Background

A. New Drug Approval Process

11. Under the FDCA, all new prescription drugs must obtain FDA approval before they can enter the marketplace. 21 U.S.C. § 355(a). The FDCA permits three types of applications for a new

drug. At one end of the spectrum, a manufacturer can submit a full New Drug Application ("NDA") under Section 505(b)(1) of the FDCA. 21 U.S.C. § 355(b)(1). A full NDA is a comprehensive application used by brand-name or innovator companies. It contains results of well-controlled scientific studies conducted by or for the applicant, demonstrating that the drug is safe and effective.

12. At the other end of the spectrum is the Abbreviated New Drug Application ("ANDA") under Section 505(j) of the FDCA. 21 U.S.C. § 355(j). ANDAs are used to obtain approval for generic versions of innovator drugs and generally do not include new clinical data. Instead, an ANDA relies on FDA's finding of safety and efficacy for a previously approved drug, which is known as the Reference Listed Drug ("RLD"). In other words, the point of an ANDA is not to demonstrate safety or effectiveness but to establish that the generic product is equivalent to an RLD already known to be safe and effective. *See* 21 U.S.C. § 355(j)(2).

13. Between the two extremes of a full NDA and an ANDA lies a third option: an application submitted under Section 505(b)(2) of the FDCA. 21 U.S.C. § 355(b)(2). A 505(b)(2) application is a type of NDA and must directly demonstrate that the proposed drug product is safe and effective. At the same time, a 505(b)(2) applicant does not have to conduct all of the burdensome scientific studies required of a full NDA. Instead, the 505(b)(2) applicant can show safety and effectiveness by relying on studies that were not conducted by the applicant and for which the applicant does not have a right of reference.

14. A 505(b)(2) application generally is used to seek approval of a drug that differs from a previously approved drug product. For example, a 505(b)(2) application may be used to seek approval of a drug product that has a different dosage form than the RLD. *See* Ex. 11, FDA Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (October 1999) at 4. In this example, the

applicant can rely on the investigative studies that were performed to obtain FDA approval for the previously approved product and new information needed to demonstrate the safety and effectiveness of the different dosage form. *Id.* at 3.

15. A 502(b)(2) applicant may rely on published literature and, similar to an ANDA, FDA's finding of safety and effectiveness for a previously approved drug product. With respect to previously approved drug products, however, FDA has stated that a 505(b)(2) applicant may not rely on a product previously approved under an ANDA because technically there is no finding of safety and effectiveness for an ANDA. *See* Ex. 12, Excerpt from FDA Clinical Review for NDA 202880 (Jan. 15, 2013) at 15.

B. Hatch-Waxman Patent Certification and Notice Process

16. Abbreviated applications both hasten the approval of new drugs and avoid unnecessary scientific testing by allowing the applicant to rely on what is already known about a drug. To balance the fact that ANDA and 505(b)(2) applicants can rely on data generated by innovator companies, Congress provided intellectual property protections for innovator products. In particular, the Hatch-Waxman amendments of 1984 create a process intended to ensure that patents covering an innovator drug are protected and that the innovator company receives notice of a relevant ANDA or 505(b)(2) application so that a patent infringement action can be initiated before the application is approved.

17. When a drug is approved under an NDA, including a 505(b)(2) application, the drug and related patents are listed in an FDA publication called *Approved Drug Products with Therapeutic Equivalence Evaluations* (34th Ed. 2014), known as the "*Orange Book*." If the product is the first-approved innovator of its kind, FDA will designate the product as the RLD for similar products. See

21 C.F.R. § 314.3(b) ("Reference listed drug means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application.").

18. When an applicant submits an ANDA, the application must identify the RLD on which the application relies. *See* 21 U.S.C. § 355(j)(2)(A)(i). Similarly, when an applicant submits a 505(b)(2) application, the application must identify the previously approved drug relied upon for approval, if any. 21 C.F.R. § 314.54.

19. ANDAs and 505(b)(2) applications also must include certifications to the patents listed in the *Orange Book* for the referenced drug. *See* 21 U.S.C. §§ 355(b)(2)(A), 355(j)(2)(A)(vii). The applicant must certify that (i) no such patents exist, (ii) any such patents have expired, (iii) the proposed drug will not be marketed before the patent expires, or (iv) any such patents are invalid or will not be infringed by the proposed drug. *See, e.g.*, 21 U.S.C. § 355(b)(2)(A)(i) through (iv).

20. An ANDA or 505(b)(2) applicant that seeks FDA approval before a patent expires generally must submit a "Paragraph IV" certification – in keeping with paragraph iv of the statutory provision – asserting that the patent is invalid or will not be infringed. Critically, whenever such an applicant submits a Paragraph IV certification, the applicant must promptly give notice to the manufacturer of the referenced drug and (to the extent there is a difference) to the owner of the relevant patents. *See, e.g.*, 21 U.S.C. § 355(b)(3)(A). Notice of a Paragraph IV certification must include certain information regarding the application and the reasons why the patent is invalid or not infringed. *Id.* § 355(b)(3)(D).

21. A Paragraph IV notice vests important statutory rights in the recipients. The submission of an ANDA or 505(b)(2) application seeking FDA approval during the term of a relevant patent is a technical act of patent infringement. *See* 35 U.S.C. § 271(e). If the patent holder or drug

manufacturer brings an infringement action against the applicant within 45 days of receiving notice of the patent certification, FDA is statutorily prohibited from approving the application until 30 months have passed, the patents have expired, or a court has found the patents invalid or not infringed. See 21 U.S.C. §§ 355(c)(3)(C), 355(j)(5)(B)(iii).

II. Factual Background

A. Takeda's Colycrys®

22. On July 29, 2009, FDA approved Colcrys® oral tablets in 0.6 mg strength for the treatment of Familial Mediterranean Fever ("FMF"). Because FMF is a rare disease, Mutual Pharmaceutical Company Inc. ("Mutual") – the company that developed Colcrys® and then transferred rights to the product to Takeda – received for that indication seven years of orphan drug exclusivity, which expires on July 29, 2016. 21 U.S.C. § 360cc. On July 30, 2009, FDA approved Colcrys® for the treatment of acute gout flares, and on October 16, 2009, it approved the drug for prophylaxis of gout flares. Mutual used the 505(b)(2) pathway to obtain approval for Colcrys®, relying on its own clinical trials, literature, and a previously approved drug product. FDA designated Colcrys® as an RLD, and it is the only single-ingredient colchicine product designated as an RLD.

23. As a result of Mutual's innovative development to support the approval of Colcrys®, Mutual has obtained numerous patents directed to colchicine. In total, there are 17 patents listed in FDA's *Orange Book* for Colcrys®.

24. Colcrys® was the first single-ingredient oral colchicine product to receive marketing approval from FDA. Ex. 3, FDA Alert, *Information for healthcare Professionals: New Safety Information for Colchicine (marketed as Colcrys)* (July 30, 2009). Although other single-ingredient

oral colchicine products were marketed before the approval of Colcrys®, such products were marketed without approved applications. *Id.*

25. Colchicine is a known toxin, and colchicine-containing drug products can have serious side effects if not properly administered. Prior to Colcrys®'s approval, oral colchicine tablets were sold by various manufacturers without approved applications and were associated with significant adverse events, including death. *Id.*; Ex. 4, 75 Fed. Reg. 60769 (Oct. 1, 2010). FDA was made aware of 751 reports of adverse events associated with colchicine toxicity, including 169 deaths associated with oral colchicine. *Id.* Of the 169 deaths, 117 were not reported as overdoses. In other words, the majority of reported deaths had colchicine doses within the normal therapeutic range. Ex. 3 at 2. Furthermore, 60 of the 117 non-overdose reported deaths (51%) involved patients who were concomitantly using another drug called clarithromycin, indicating that drug-drug interactions may be related to toxicity. Id.

26. To support the safety and efficacy of Colcrys®, Mutual conducted two critical sets of clinical studies with the goal of reducing colchicine toxicity and related fatalities. Ex. 3. First, Mutual studied drug-drug interactions. *Id.* Second, Mutual studied whether a lower colchicine dose could be effective to treat gout flares. *Id.*

27. To study drug-drug interactions, Mutual conducted at least eight studies comparing the bioavailability of colchicine administered alone with the bioavailability of colchicine co-administered with other drugs. *Id.* Such drugs included cytochrome P450 3A4 ("CYP3A4") inhibitors, protease inhibitors, and P-glycoprotein ("P-gp") inhibitors, all of which can block the mechanisms that the body uses to break down colchicine and, thus, can lead to toxic amounts of colchicine.

28. Mutual discovered that co-administering colchicine and such drugs significantly raises colchicine levels in the blood. Ex. 5, Colcrys® Label. For example, the co-administration of clarithromycin, a commonly used antibiotic, can cause colchicine blood levels to increase by approximately 250% percent. *Id.* Based on its studies, Mutual also developed a safe way to dose colchicine concomitantly with such drugs, including clarithromycin. *Id.* The dose adjustments are critically important from a public health perspective. In particular, as noted above, 51% of the deaths attributed to oral colchicine taken within therapeutic limits involved patients who were concomitantly using clarithromycin. Ex. 3.

29. Based on Mutual's drug-drug interaction studies, the label for Colcrys® includes several detailed tables that provide specific dose adjustments for patients who take colchicine with CYP3A4 inhibitors, P-gp inhibitors, or protease inhibitors. Ex. 5 at 5-6. In its review of Colcrys®, FDA stated that the new dose adjustments are "necessary" to compensate for the increase in colchicine exposure. In particular, FDA stated:

> *Strong CYP3A4 inhibitors increase colchicine systemic exposure by 3- to 4-fold. Hence, a 75% decrease in dose is necessary to compensate for the increase in exposure.*
>
> *Moderate CYP3A4 inhibitors cause a 2-fold increase in colchicine AUC when coadministered. Hence, a 50% decrease in dose is necessary to compensate for the increase in exposure.*
>
> *P-gp inhibition by cyclosporine resulted in 3.5-fold increase in Cmax and AUC of colchicine. Hence, a 75% decrease in dose is necessary to compensate for the increase in exposure.*

Ex. 6, FDA Clinical Pharmacology and Biopharmaceutics Review(s) for Colcrys NDA 22-353at 10-11 (August 17, 2009) (underlining added).

30. Underscoring the importance of Mutual's work, FDA issued an FDA Alert when Colcrys® was approved to inform healthcare providers and the general public of the significant new safety information regarding the administration of colchicine. The FDA Alert notes that the Colcrys®

label contains dose adjustments to reduce the risk of drug-drug interactions and recommends that healthcare professionals "refer to Colcrys' approved prescribing information for specific dosing recommendations and additional drug interaction information." Ex. 3 at 1.

31. Mutual's work in identifying and resolving potentially fatal drug-drug interactions for colchicine has been deemed so important by FDA that FDA incorporated it into the labeling for other drugs as well. In particular, one of Mutual's studies demonstrated that the co-administration of colchicine with the protease inhibitor ritonavir could increase colchicine blood levels by nearly 185%. Ex. 5. As a result of this work, FDA took the significant step of requiring the labeling for all protease inhibitors approved for the treatment of HIV-1 infection (such as Norvir (ritanovir) and Invirase (saquinavir mesylate)) to include Mutual's reduced dosing recommendations for co-administering these drugs with colchicine. Ex. 7, FDA Protease Inhibitor Statement.

32. In addition to drug-drug interactions, Mutual also studied whether a low-dose regimen is effective for the treatment of acute gout flares. Ex. 5. Historically, the recommended dose of colchicine for the treatment of acute gout flares was 1.2 mg of colchicine followed by 0.6 mg every hour until the flare resolved or until gastrointestinal toxicity occurred, a regimen that could result in a total dose of about 4.8 mg. Ex. 3 at 2. In contrast, Mutual developed a low-dose regimen consisting of 1.2 mg followed by 0.6 mg one hour later, which provides a total dose of 1.8 mg. Id.

33. Mutual designed and conducted a multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-comparison trial in which 185 adults (out of a total of 575 trial participants) were exposed to a high dose regimen of colchicine, low dose of colchicine, or placebo. Ex. 8, Medical Review of NDA 22-351. Mutual's trial was referred to as the Acute Gout Flare Receiving Colchicine Evaluation ("AGREE") Trial. *Id.*

34. AGREE demonstrated that Mutual's new low-dose regimen for Colcrys® is effective for gout flares and reduces the risk of adverse events compared to the traditional high-dose regimen. Ex. 8. For example, ten trial participants receiving the high dose of colchicine experienced serious adverse events, while *zero* participants receiving the low dose of colchicine did so. *Id.* As another example, the rate of less-severe gastro-intestinal adverse events (e.g., diarrhea, nausea or vomiting) was just 26% in low-dose subjects compared to 77% in high-dose subjects. *Id.* AGREE showed that patients have historically been given between two and four times the necessary colchicine dosage to achieve the desired effect. *Id.* FDA highlighted the significant safety improvement provided by Mutual's new low-dose regimen in its FDA Alert. Ex. 3 at 3.

B. Hikma's Mitigare

35. During the fall of 2010, Mutual learned through public sources that Hikma's U.S. manufacturer, West-Ward Pharmaceutical Corp., had submitted an application to FDA for a single-ingredient oral colchicine product. The FDA application process is confidential, and Mutual did not know the details of the application. However, Mutual surmised that West-Ward's application was for a duplicate generic version of Colcrys®. Accordingly, Mutual expected to be cited as the RLD for West-Ward's application and expected to receive a patent certification notice. Even if West-Ward's application was not for a duplicate version of Colcrys®, Mutual still expected that Colcrys® would be cited as a reference drug because the application would have to rely on the new drug-drug interaction and low-dose information developed by Mutual.

36. Mutual did not receive any notice of patent certification.

37. Accordingly, in November 2010, Mutual filed a Citizen Petition with FDA requesting that FDA ensure that any application seeking approval for a duplicate version of Colcrys® be

submitted as an ANDA and not a 505(b)(2) application. Ex. 9, Mutual Citizen Petition, Docket No. FDA-2010-P-0614 at 2 (Nov. 26, 2010). Mutual's Citizen Petition requested, among other items, that FDA "[r]equire the labeling for any single ingredient oral colchicine product to include all information related to drug-drug interactions that is in the Colcrys® labeling, including relevant dose adjustments needed to prevent unnecessary toxicity." *Id.* at 2.

38. FDA granted the major actions requested in Mutual's Citizen Petition. Ex. 1. FDA confirmed that West-Ward had inappropriately submitted a 505(b)(2) application for a duplicate version of Colcrys®, and that the application must be withdrawn and resubmitted as an ANDA. *Id.*

39. FDA also agreed with Mutual regarding the critical importance of the drug-drug interaction information Mutual had developed. *Id.* Specifically, FDA stated that "FDA agrees that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity." Ex. 1 at 3. After noting the risk for severe drug interactions, FDA concluded that the new dosing recommendations will help mitigate the risk. *Id.* at 19. Importantly, FDA acknowledged that:

> Before the approved labeling for Colcrys, there were no widely-accepted specific recommendations for dose reduction in the setting of potential concomitant use of drugs with known interactions, other than avoidance when possible and caution when necessary, with vigilant monitoring of clinical signs of toxicity.

Ex. 1 at 19.

40. Furthermore, FDA concluded that the labeling for *any* single-ingredient colchicine product for prophylaxis of gout flares must include the new low-dose regimen for treating acute gout flares because prophylactic patients may develop an acute gout flare and the new low dose is essential

to avoiding cumulative toxicity from combining the treatments for prophylaxis and acute gout flares. In particular, FDA stated:

> To the extent that a healthcare provider determines it is necessary to use colchicine for treatment of an acute gout flare in a patient receiving colchicine for prophylaxis, adequate information about potential toxicity of colchicine dosing would be important to minimize the risk of cumulative toxicity. Accordingly, the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares should inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine use.

Ex. 1 at 24 (footnotes omitted).

41. Over three years passed. Then, without notice or warning, on September 26, 2014, FDA approved Hikma's colchicine product, Mitigare, which is a 0.6 mg oral capsule. Ex. 10, Letter from B. Chowdhury to Hikma Pharmaceuticals LLC (Sept. 26, 2014) at 1. Takeda became aware of the approval on September 30, 2014 from a Hikma press release of that date. Mitigare is indicated only for the prophylaxis of gout flares. *Id.* According to FDA's approval letter, Mitigare was submitted under a 505(b)(2) application. *Id.* As a capsule, Mitigare is not an exact duplicate of Colcrys®. Apparently, instead of resubmitting its previous application for a duplicate colchicine product as an ANDA, Hikma reformulated the product to have a different dosage form and submitted it – again – under a 505(b)(2) application.

42. Despite FDA's response to Mutual's Citizen Petition, the label for Mitigare does not include the Colcrys® drug-drug interaction dose adjustments. Rather, the label for Mitigare states:

> Inhibition of both CYP3A4 and P-gp by dual inhibitors such as clarithromycin has been reported to produce life-threatening or fatal colchicine toxicity due to significant increases in systemic colchicine levels. Therefore, concomitant use of MITIGARE™ and inhibitors of CYP3A4 or P-glycoprotein should be avoided [See Drug Interactions (7)]. If avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity.

Ex. 2 at 2.

43. Similarly, the label for Mitigare also omits Colcrys®'s low-dose regimen for treating acute gout flares. *Id.* Although Mitigare is not indicated for acute gout flares, FDA specifically concluded that even a single-ingredient colchicine product indicated only for prophylaxis still must include the low-dose regimen for acute gout flares because of the potential for cumulative toxicity when treating patients for both prophylaxis and acute flares. Colcrys Response at 24. Nonetheless, the label for Mitigare simply states that "[t]he safety and effectiveness of MITIGARE™ for acute treatment of gout flares during prophylaxis has not been studied." Ex. 2 at 1, 2.

44. As with the previous 505(b)(2) application, Hikma apparently did not reference Colcrys® because the Mitigare label omits the new safety innovations developed for Colcrys®. Thus, the application did not include any certification to the patents listed for Colcrys®, which allowed Hikma to avoid the notification and 30-month stay provisions. And because the FDA application process otherwise is confidential, the first that Takeda – Mutual's corporate successor – learned of Mitigare's approval was following the September 26 approval letter itself. *See* Confid. Decl. of Mathew Woods.

45. On or around October 3, 2013, Hikma launched Mitigare as a brand-name colchicine drug that would complete with Colcrys®. Upon information and belief, Hikma does not intend to market Mitigare as a branded drug, but instead plans to authorize one of its subsidiaries to manufacture and sell a generric version of Mitigare on its behalf. *See id.*

III. FDA's Conduct is Unlawful, Arbitrary and Capricious

46. FDA's approval of Hikma's 505(b)(2) application for Mitigare violates the FDCA and applicable regulations, including but not limited to 21 U.S.C. § 355(b)(1), 21 U.S.C. § 355(b)(2), 21

U.S.C. § 355(b)(3), 21 U.S.C. § 355(d), 21 C.F.R. § 314.50, 21 C.F.R. § 314.52, 21 C.F.R. § 314.54, 21 C.F.R. § 314.105, 21 C.F.R. § 314.125.

47. Among other things, FDA acted arbitrarily and capriciously by approving Hikma's Mitigare product without the critical safety information that FDA previously had expressly found to be necessary for single-ingredient oral colchicine products. As noted, the Mitigare label does not include the low-dose regimen for acute gout flares that is an integral part of the Colcrys® label. Ex. 2. Even though Mitigare is indicated only for prophylaxis, FDA has clearly stated that the labeling for a prophylaxis product must disclose the dosage for treatment of an acute gout flare due to the risk of cumulative toxicity:

> To the extent that a healthcare provider determines it is necessary to use colchicine for treatment of an acute gout flare in a patient receiving colchicine for prophylaxis, adequate information about potential toxicity of colchicine dosing would be important to minimize the risk of cumulative toxicity. **Accordingly, the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares should inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine use.**

Ex. 1 at 24 (emphasis added) (footnotes omitted).

48. In contrast to FDA's explicit statement, the Mitigare label simply states that Mitigare has not been studied in acute gout flares. Ex. 2 at 1, 2. By omitting the low-dose regimen for acute gout flares, Hikma was able to avoid referencing Colcrys® and certifying to the Colcrys® patents.

49. In addition, the Mitigare label does not include the specific dose adjustments to avoid potentially fatal drug-drug interactions. Tables in the Colcrys® label include specific dose adjustments, even for prophylaxis. Ex. 5 at 5-6. However, the label for Mitigare simply states that the problematic drugs should be avoided to avoid adverse drug-drug interactions or, if use is necessary,

dose should be adjusted and patients should be monitored. Ex. 2 at 2. The Mitigare label provides no specifics regarding the correct dose adjustment. *See id.*

50. Mitigare's label is in direct conflict with FDA's stated position on this issue in its Response to Mutual's Citizen Petition, which states: "FDA agrees that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, **including relevant dose adjustments needed to prevent unnecessary toxicity."** Ex. 1 at 19 (emphasis added).

51. By permitting Hikma to avoid the specific drug-drug interaction dose adjustments, FDA allowed Hikma to proceed without referencing Colcrys® and without certifying to the Colcrys® patents. *See* 21 U.S.C. § 355(b)(2)(A).

52. As discussed above, as a result of Mutual's studies regarding the co-administration of colchicines and ritonavir, (a) the Colcrys® label includes reduced dosing for co-administration with protease inhibitors, Ex. 1 at 6, and (b) the FDA required the labels for all protease inhibitors approved for the treatment of HIV-1 infection to include Mutual's reduced dosing instructions for co-administration of these drugs with colchicine. Ex. 7 at 1.

53. Mitigare's label omits the protease inhibitor dose adjustments. By omitting the dose adjustments for protease inhibitors, Hikma was able to avoid referencing Colcrys® and certifying to the Colcrys® patents.

54. FDA also acted unlawfully by approving Hikma's Mitigare product because the product fails to meet the statutory standard required for FDA approval. The FDCA prohibits FDA from approving products unless they are both safe and effective. 21 U.S.C. § 355(b)(1). As noted more fully above, Hikma's label does not include important safety information, including but not limited to

the specific dosing adjustments to reduce the risk of potentially fatal drug-drug interactions and the low-dose regimen for the treatment of gout flares. Ex. 2. In fact, Hikma's labeling resembles the labels of older colchicine products that were associated with a significant number of fatalities related to drug-drug interactions and colchicine toxicity. Ex. 2.

55. Furthermore, Mitigare creates safety issues because it cannot be easily split. Ex. 2. The reduced dosing for drug-drug interactions recommended in the Colcrys® label and the protease inhibitor labels recommend 0.3 mg doses, which is half a Colcrys® tablet or Mitigare capsule. Exs. 5, 7. Colcrys® is a scored tablet that can be easily split. Ex. 5. In contrast, Mitigare is an unscored capsule; although the *frequency* of dosage can be reduced, as compared to Colcrys it would be difficult to split a Mitigare capsule with the precision needed to get the 0.3 mg dose. Ex. 2.

56. FDA also acted arbitrary and capriciously, and contrary to law, by not requiring Hikma to reference Colcrys® and provide certifications to the patents listed for Colcrys®. Despite FDA's previous proclamation about the necessity of including drug-drug interaction dosing adjustments and low-dosage regimen safety information, the Mitigare label was devoid of that information. This action circumvented the need for Hikma to reference Colcrys® and certify to the patents listed for Colcrys®. Had Hikma certified to these patents, the patent certifications likely would have included a Paragraph IV certification, which in turn would have required Hikma to notify Takeda of the pending application. Such notice would necessarily have triggered patent litigation and consequently a statutorily mandated 30-month stay of Hikma's application. *See* FDCA §§ 505(c)(3); 505(j)(5)(B)(iii).

57. Because Hikma was not required to file a Paragraph IV certification relating to Mutual's patents, thus keeping its application confidential from Mutual and its successor Takeda, Takeda was

also deprived of the opportunity to file a Citizen's Petition in advance of Mitigare's approval. Under 20 C.F.R. § 10.30, any person or entity, including pharmaceutical companies, may file a Citizen Petition asking FDA to refrain from taking an administrative action. But here, Takeda never had the opportunity. If FDA had complied with its governing regulations and statutory mandate, Takeda would have received notice of the pending application under the Hatch-Waxman Act. Now, absent immediate intervention from this Court, it is too late. For these reasons, Takeda suffered a procedural harm at the hands of FDA that is irreparable.

58. For all of these reasons, FDA's decision to approve Hikma's 505(b)(2) application for Mitigare was not in accordance with federal law and therefore violates 5 U.S.C. § 706(2)(A).

59. For all of these reasons, FDA's decision to approve Hikma's 505(b)(2) application for Mitigare also constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

IV. FDA's Actions Will Cause Immediate and Irreparable Harm to Patients and Takeda

60. The patient population and Takeda will be irreparably harmed unless FDA's approval of Hikma's 505(b)(2) application for Mitigare is rescinded or at least stayed pending FDA's compliance with applicable law.

61. FDA's actions pose a substantial and imminent harm to prospective patients who will be placed on Mitigare. The label FDA approved for Mitigare lacks critical information regarding low-dose treatment for acute gout and the drug-drug interaction dosing adjustments, directly contradicting FDA's earlier patient safety-related labeling requirements. *See supra* ¶¶ 41-44. Before FDA approved Colcrys® and removed the unapproved products from the market, the unapproved products generally contained labeling information that lacked such safety information. Labeled in this manner,

these unapproved products were associated with a significant number of fatalities related to drug-drug interactions and colchicine toxicity. Reverting to a regime where colchicine products lack the requisite safety information would expose patients to a significantly higher risk of harm from colchicine toxicity than is necessary. Because of Hikma's ability to now launch this product at any time, the threat to patient safety is imminent.

62. FDA's actions will also irreparably harm Takeda. By failing to afford Takeda the right to file a Citizen Petition in advance of FDA's approval decision, FDA inflicted an irreparable procedural harm on Takeda.

63. Takeda also will suffer irreparable reputational harm absent entry of a temporary restraining order. Any injuries or fatalities resulting from the Mitigare label's lack of drug-drug interaction and low-dosage safety information will be unfairly imputed to Colcrys®, which would lead to reputational harm for the product and possibly to Takeda. These adverse effects on business reputation, goodwill, and relationships with physicians and patients constitute irreparable harm sufficient to warrant injunctive relief.

64. Still further, FDA's recent approval of Mitigare® means Hikma could launch this product in the market at any moment. The impact on Takeda would be commercially devastating. Takeda and its former affiliate Mutual have expended hundreds of millions of dollars to develop, patent, and promote Colcrys® to ensure proper, appropriate and safe utilization of single ingredient colchicine in patients with gout. Takeda would lose the value of its investment if a generic single-ingredient oral colchicine product were permitted to prematurely enter the market.

65. New drug entrants into the market have an immediate and precipitous effect upon both market share and the pricing of the brand name drugs upon which they are based. Takeda estimates

that if Hikma enters the market with a lower-cost colchicine drug product, within the first four weeks, Takeda would lose between 60-70% of the number of Colcrys® prescriptions that would otherwise be written and filled, and within the first twelve months Takeda would lose 95-98% of these prescriptions. That loss will result from automatic substitution at pharmacies, requests by patients and physicians, and changes in formularies and preferred drug lists across private and public sector health care plans.

66. There is no mechanism by which Takeda can be made whole for the injury that would result from the entry into the marketplace of Hikma's Mitigare drug. And because the foregoing losses never can be recovered from FDA, Takeda will be irreparably harmed unless FDA's conduct is enjoined promptly. *See, e.g.*, *Clarke v. Office of Fed. Hous. Enterprise Oversight*, 355 F. Supp. 2d 56, 65-66 (D.D.C. 2004) (holding that economic losses constitute irreparable injury where they are unrecoverable due to government immunity).

67. The intent of Congress will be served by an Order directing FDA to rescind – or at least stay pending compliance with the proper regulatory process – its approval of Hikma's 505(b)(2) application for Mitigare. In addition, the public interest will be served by such an Order.

68. FDA's approval of Hikma's 505(b)(2) application for Mitigare constitutes final agency action for which Takeda has no other adequate remedy within the meaning of 5 U.S.C. § 704.

Count I
(Administrative Procedure Act: Violation of the FDCA and Applicable Regulations)

69. Takeda realleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 68 of the Verified Complaint as though set forth fully herein.

70. FDA's approval of Hikma's 505(b)(2) application for Mitigare was unlawful and in violation of the FDCA and the agency's own regulations, policies and procedures.

71. FDA's approval of Hikma's 505(b)(2) application for Mitigare constitutes final agency action for which Takeda has no other adequate remedy within the meaning of 5 U.S.C. § 704.

72. FDA's approval of Hikma's 505(b)(2) application for Mitigare was not in accordance with federal law and therefore violates 5 U.S.C. § 706(2)(A).

73. FDA's approval of Hikma's 505(b)(2) application for Mitigare constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

74. Both Takeda and the patient population will be irreparably harmed unless FDA is required to withdraw its approval of Hikma's 505(b)(2) application for Mitigare.

75. There is no mechanism by which Takeda can be made whole for the injury that would result from the entry into the marketplace of an unlawful colchicine product. Takeda is without an adequate remedy at law because of the unique nature of the harm.

76. The intent of Congress will be served by an Order directing FDA to withdraw its approval of Hikma's 505(b)(2) application for Mitigare. In addition, the public interest will be served by such an Order.

Count II
(Administrative Procedure Act: FDA's Conduct Was Arbitrary, Capricious, an Abuse of Discretion and Contrary to Law)

77. Takeda realleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 68 of the Verified Complaint, as though set forth fully therein.\

78. The APA prohibits FDA from implementing the FDCA in a manner that is arbitrary, capricious, or an abuse of discretion. 5 U.S.C. § 706(2)(A).

79. FDA's approval of Hikma's 505(b)(2) application for Mitigare was not based on reasoned decision or rational basis, and therefore was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

80. FDA's approval of Hikma's 505(b)(2) application for Mitigare was premised on agency determinations that represented abrupt departures from long-standing agency practice and the treatment of similarly-situated entities differently. FDA's conduct was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

81. FDA's approval of Hikma's 505(b)(2) application for Mitigare violates FDA's own regulations and governing statute, in violation of the APA.

82. FDA's approval of Hikma's 505(b)(2) application for Mitigare constitutes final agency action for which Takeda has no other adequate remedy within the meaning of 5 U.S.C. § 704.

83. Both Takeda and the patient population will be irreparably harmed unless FDA is required to withdraw its approval of Hikma's application.

84. There is no mechanism by which Takeda can be made whole for the injury that would result from the entry into the marketplace of Hikma's product. Takeda is without an adequate remedy at law because of the unique nature of the harm.

85. The intent of Congress will be served by an Order directing FDA to withdraw its approval of Hikma's 505(b)(2) application for Mitigare. In addition, the public interest will be served by such an Order.

PRAYER FOR RELIEF

WHEREFORE, plaintiff respectfully prays for the following relief:

A. A declaration pursuant to 28 U.S.C. § 2201 that FDA's approval of Hikma's 505(b)(2) application for Mitigare was arbitrary, capricious, and unlawful under the APA and the FDCA;

B. A declaration pursuant to 28 U.S.C. § 2201 that FDA's refusal to require Hikma's 505(b)(2) application to reference Colcrys® was arbitrary, capricious, and unlawful under the APA and the FDCA;

C. A declaration pursuant to 28 U.S.C. § 2201 that FDA's actions, findings, and conclusions in approving Hikma's 505(b)(2) application for Mitigare were arbitrary, capricious, an abuse of discretion, and without factual basis;

D. Temporary, preliminary and permanent injunctive relief requiring FDA to rescind or – at the very least – stay its approval of Hikma's 505(b)(2) application for Mitigare;

E. An order awarding plaintiff's costs, expenses and attorneys fees pursuant to 28 U.S.C. § 2412; and

F. Such other and further relief as the Court deems just and proper.

Respectfully submitted,

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Attorneys for Plaintiff Takeda Pharmaceuticals U.S.A., Inc.

Dated: October 6, 2014

VERIFICATION

I, the undersigned, having read the allegations of the foregoing Verified Complaint, hereby declare under penalty of perjury and pursuant to 28 U.S.C. § 1746 that the factual allegations asserted in the Verified Complaint are true and correct based on my personal knowledge and on information derived from the business records of Takeda Pharmaceuticals U.S.A., Inc. I further declare that matters asserted upon information and belief are believed to be true and correct.

Executed this 6th day of October, 2014.

Matthew Woods