IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICALS U.S.A., INC., Plaintiff, v. GRANULES PHARMACEUTICALS INC., Defendant.	Civil Action No. 17-1019-RGA

FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") files this Complaint for patent infringement against Defendant Granules Pharmaceuticals Inc. ("Granules") and, in support thereof, alleges as follows.

NATURE OF THE ACTION

1. This is an action for patent infringement under the Food and Drug and Patent Laws of the United States, U.S.C. Titles 21 and 35 respectively, arising from Granules's submission of Abbreviated New Drug Application ("ANDA") No. 210425 (the "Granules ANDA") to the United States Food and Drug Administration ("FDA"), seeking approval to sell commercially a generic version of the drug product Colcrys® (colchicine, USP) (the "ANDA Product") prior to the expiration of United States Patent Nos. 7,906,519; 7,935,731; 8,093,298; 7,964,648; 8,093,297; which cover, *inter alia*, methods of using colchicine for treating and preventing gout flares and treating Familial Mediterranean Fever.

THE PARTIES

2. Takeda Pharmaceuticals U.S.A., Inc. is a Delaware corporation with its principal place of business at One Takeda Parkway, Deerfield, IL 60015. Takeda holds all right, title and interest in each patent asserted in this action.

3. On information and belief, Granules is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3701 Concorde Parkway, Chantilly, Virginia, 20151.

4. On information and belief, Granules is registered to do business as a domestic corporation in Delaware (File Number 5625226).

5. On information and belief, Granules has designated its registered agent for the receipt of service of process for the State of Delaware as VCorp Services, LLC, 1013 Centre Road Suite 403-B, Wilmington, Delaware, 19805.

6. On information and belief, Granules is in the business of making and selling generic pharmaceutical products, which it distributes in the State of Delaware and throughout the United States.

JURISDICTION AND VENUE

7. This action for patent infringement arises under 35 U.S.C. § 271.

8. This Court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a), and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

9. This Court has personal jurisdiction over Granules. On information and belief, Granules has extensive contacts with the State of Delaware. Granules is a corporation organized and existing under the laws of the State of Delaware. Granules is registered to do business in Delaware (File Number 5625226). Granules has designated its registered agent for the receipt of

service of process for the State of Delaware as VCorp Services, LLC, 1013 Centre Road Suite 403-B, Wilmington, Delaware, 19805.

10. On information and belief, Granules regularly does business in Delaware by selling and distributing generic pharmaceutical products. On information and belief, Granules directly, or through its affiliates and agents, formulates, manufactures, packages, markets, and/or sells pharmaceutical products throughout the United States and in Delaware. On information and belief, Granules derives substantial revenue from products sold or consumed in Delaware.

11. Granules has filed an ANDA with the FDA for a generic drug product, which indicates Granules's intention to sell that product throughout the United States, including in Delaware. If the Granules ANDA is approved, its ANDA Product will, among other things, be marketed and distributed in Delaware, and/or prescribed by physicians practicing in Delaware and dispensed by pharmacies located within Delaware, all of which will have a substantial effect on Delaware. Granules knows and intends that its ANDA Product will be distributed and sold in the United States, including in Delaware. If Granules is permitted to market its ANDA Product, Takeda will be specifically harmed by Granules's sales of its ANDA Product, including its sales in Delaware.

12. Venue is proper in this District under 28 U.S.C. § 1400(b) and/or 28 U.S.C. § 1391(b).

STATEMENT OF FACTS RELEVANT TO ALL COUNTS

13. Takeda is the holder of New Drug Application ("NDA") Nos. 22-351, 22-352, and 22-353, pursuant to which the FDA granted approval in 2009 for the commercial manufacturing, marketing, sale, and use of Colcrys® (colchicine, USP) tablets, 0.6 mg, pursuant to section 505(b) of the Federal Food Drug and Cosmetics Act ("FFDCA"), 21 U.S.C. § 355(b).

14. Colcrys® is primarily used to prevent and treat gout flares. Gout is a type of severe arthritis typically characterized by extremely painful "flares" (severe and sudden attacks of pain, redness, inflammation, and tenderness in joints) resulting from a build-up of uric acid. Colcrys® and Takeda's authorized generic of Colcrys® are the only oral single-active-ingredient colchicine products approved by the FDA for the treatment and prevention of gout flares.

15. Colcrys® is also used to treat Familial Mediterranean Fever ("FMF"). FMF is a rare, autosomal recessive, auto-inflammatory disease characterized by recurrent and/or chronic inflammation. Colcrys® and Takeda's authorized generic of Colcrys® are the only single-active-ingredient oral colchicine products currently on the market to treat FMF.

16. As part of the FDA approval for Colcrys®, Takeda received Orphan Drug exclusivity, which expired July 29, 2016.

17. At the time the FDA granted approval to Colcrys® in 2009, the NDA holder was Takeda's predecessor-in-interest, Mutual Pharmaceutical Company, Inc. ("Mutual"). Mutual conducted groundbreaking research, discovering important new information about colchicine, including previously unknown information concerning safety and efficacy, tolerability, dangerous side effects, and interactions with other medicines and substances.

18. Before Colcrys®, no oral single-ingredient colchicine had been reviewed by the FDA for safety and efficacy. The lack of FDA-reviewed data regarding oral single-ingredient colchicine was particularly troublesome because colchicine is potentially toxic. Before Mutual introduced Colcrys®, oral colchicine had been associated with more than 160 deaths. Accordingly, to support the safe and effective use of an oral single-ingredient colchicine product, Mutual developed its own formulation and studied the effects of that formulation in human subjects.

19. One of Mutual's clinical studies, the Acute Gout Flare Receiving Colchicine Evaluation ("AGREE") trial, provided important new information on the optimal dose of colchicine for treatment of gout flares. Traditionally, oral colchicine had been used for the treatment of gout flares by administering an initial dose of one to two 0.6 mg tablets at the onset of the flare, followed by additional doses every one to two hours until either the pain subsided or "nausea, vomiting, or diarrhea" developed. Many patients following this regimen would take a total dose of up to 8 mg of colchicine, which frequently led to toxicity-related side effects such as diarrhea or vomiting.

20. The AGREE trial completely upended the conventional wisdom. The trial was a double-blind, placebo-controlled, multicenter, dose-comparison study involving 575 trial participants. It compared the effects of the "traditional" dose described above to a lower dose of just 1.8 mg total of colchicine, administered as 1.2 mg colchicine followed by 0.6 mg 1 hour later. The AGREE trial proved that the lower-dose regimen is just as effective as the traditional higher-dose regimen but without the serious adverse events of the higher dose. Based on Mutual's trial, the FDA approved Mutual's colchicine product with the low-dose regimen as safe and effective for the treatment of gout flares. The Colcrys® low-dose regimen is recited in the FDA-approved product label attached as Exhibit A.

21. In 2012, the American College of Rheumatology ("ACR") issued guidelines for management of gout. The ACR guidelines adopt Takeda's low-dose regimen. The ACR recommends treating an acute gout flare by using a loading dose of 1.2 mg of colchicine, followed by 0.6 mg 1 hour later, and then, 12 hours later, resuming 0.6 mg prophylactic dosing once or twice daily, unless dose adjustment is necessary. The ACR recommendation remains the standard of care for the use of colchicine to treat acute gout flares. Part II of the ACR guidelines,

addressing therapy and prophylaxis of acute gouty arthritis, is attached as Exhibit B. *See* Ex. B at 1453.

22. Mutual also conducted multiple studies regarding potential adverse drug interactions involving colchicine. Mutual researched numerous drug interactions that could result in unsafe levels of colchicine and even death. Mutual discovered, for example, that co-administering colchicine with clarithromycin could increase colchicine blood levels by nearly 230%, creating a risk of toxicity. Mutual identified potentially dangerous interactions between colchicine and several other drugs, and it recommended colchicine dosing reductions to reduce the risk of an adverse reaction when colchicine is administered concomitantly with such other drugs. This dose adjustment information is currently included in the approved labeling for Colcrys®, which specifies appropriate dose adjustments when Colcrys® is co-administered with ketoconazole, verapamil, ritonavir, clarithromycin, and other drugs. *See, e.g.*, Ex. A at Table 1; *see also* Ex. B at 1453 (ACR Guidelines recommending dose adjustments in Colcrys labeling).

TAKEDA'S COLCRYS® PATENTS

23. Takeda is the lawful owner of all right, title, and interest in and to the following United States patents, including the right to sue and to recover for infringement thereof, which contain one or more claims covering methods of using Colcrys®.

A. United Sates Patent Number 7,906,519 ("the '519 Patent"), entitled "METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT," a copy of which is attached hereto as Exhibit C and incorporated herein by reference as though set forth in full, which was duly and legally issued March 15, 2011, naming Matthew Davis as the inventor.

B. United States Patent Number 7,935,731 ("the '731 Patent"), entitled "METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE

AND MACROLIDE ANTIBIOTICS," a copy of which is attached hereto as Exhibit D and incorporated herein by reference as though set forth in full, which was duly and legally issued May 3, 2011, naming Matthew Davis as the inventor.

C. United States Patent Number 8,093,298 ("the '298 Patent"), entitled "METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS," a copy of which is attached hereto as Exhibit E and incorporated herein by reference as though set forth in full, which was duly and legally issued January 10, 2012, naming Matthew Davis as the inventor.

D. United States Patent Number 7,964,648 ("the '648 Patent"), entitled "METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT," a copy of which is attached hereto as Exhibit F and incorporated herein by reference as though set forth in full, which was duly and legally issued June 21, 2011, naming Matthew Davis as the inventor.

E. United States Patent Number 8,093,297 ("the '297 Patent"), entitled "METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT," a copy of which is attached hereto as Exhibit G and incorporated herein by reference as though set forth in full, which was duly and legally issued January 10, 2012, naming Matthew Davis as the inventor.

24. The '519, '731, '298, '648 and '297 Patents are collectively referred to herein as the "FMF Patents."

25. The above-listed patents—together with U.S. Patent Nos. 7,619,004; 7,601,758; 7,820,681; 7,915,269; 7,964,647; 7,981,938; 8,093,296; 8,097,655; 8,415,395; 8,415,396; 8,440,721; and 8,440,722—are collectively referred to herein as the "Colcrys® Patents."

26. The Colcrys® Patents are listed in the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly referred to as the "Orange Book") as patents "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1).

GRANULES'S ACTIONS GIVING RISE TO THIS SUIT

27. Granules submitted ANDA No. 210425 to the FDA seeking approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of 0.6 mg oral colchicine tablets (i.e., Granules's ANDA Product) prior to the expiration of Takeda's patents relating to Colcrys®.

28. On or about June 23, 2017, Takeda received a letter dated June 23, 2017 notifying Takeda of Granules's submission to the FDA of ANDA No. 210425, seeking approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of Granules's ANDA Product to treat FMF and containing a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certification") with respect to, *inter alia,* the '519, '731, '298, '648, and '297 Patents (hereinafter, the "Paragraph IV Notice Letter"). Granules asserted in its Paragraph IV Notice Letter that it is entitled to bring its product to market prior to the expiration of Takeda's '519, '731, '298, '648, and '297 Patents because those patents are invalid, unenforceable, and/or would not be infringed.

29. Granules's Paragraph IV Notice Letter included a detailed statement of the factual and legal basis for the certifications set forth in Granules's ANDA. Granules's Paragraph IV Notice Letter set forth Granules's positions regarding the invalidity of the '519, '731, '298, '648, and '297 Patents and regarding Granules's non-infringement of the '731 and '298 patents.

30. Granules's Paragraph IV Notice Letter also included an offer to the patentee of confidential access pursuant to 21 U.S.C. § 355G)(5)(C). Takeda accepted Granules's offer of confidential access, and counsel for Takeda reviewed portions of Granules's ANDA No. 210425 before bringing this infringement action.

31. Granules's Paragraph IV Notice Letter did not state that Granules is seeking approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of its ANDA Product for the treatment or prevention of gout flares. Takeda is informed and believes the Granules has submitted a statement under 35 U.S.C. § 355(j)(2)(A)(viii) ("section viii carve-out") to the FDA with respect to those of Takeda's Colcrys® Patents directed to the treatment or prevention of gout.

32. Takeda commenced this action within 45 days of receiving Granules's Paragraph IV Notice Letter.

GRANULES'S INFRINGEMENT OF THE FMF PATENTS

33. Takeda's FDA approved product label for Colcrys® teaches and encourages, *inter alia*, methods of using Colcrys® claimed in the FMF Patents, including the use of colchicine to treat FMF when a patient is or is not taking another substance. *See, e.g.*, Ex. A at Table 1.

34. Under the FFDCA, drug products submitted to the FDA for approval via an ANDA are required to have the same labeling as the reference listed drug, here Colcrys®, except for changes required because of differences approved under a suitability petition (21 U.S.C. § 355(j)(2)(C); 21 C.F.R. § 314.93), because the generic drug product and reference listed drug are produced or distributed by different manufacturers (21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. §314.94(a)(8)(iv)), or because the ANDA applicant has made a section viii carve-out for one of the indications on the label of the reference listed drug.

35. The approved labeling for Colcrys® recites the claimed methods of Takeda's FMF Patents. The Colcrys® labeling states that "[c]o-administration of COLCRYS with drugs known to inhibit CYP3A4 and/or P-glycoprotein (P-gp) increases the risk of colchicine-induced toxic effects (Table 1). If patients are taking or have recently completed treatment with drugs listed in Table 1 within the prior 14 days, the dose adjustments are as shown on the table below [see DRUG INTERACTIONS (7)]." *See* Ex. A § 2.4; *see also id.* § 7 ("Table 1 provides recommendations for strong and moderate CYP3A4 inhibitors and P-gp inhibitors."). Table 1 is reproduced in part below:

Table 1
COLCRYS Dose Adjustment for Co-administration with Interacting Drugs if no Alternative Available[1]

Strong CYP3A4 Inhibitors[2]							
Drug	**Noted or Anticipated Outcome**	**Gout Flares**				**FMF**	
		Prophylaxis of Gout Flares		**Treatment of Gout Flares**			
		Original Intended Dosage	**Adjusted Dose**	**Original Intended Dosage**	**Adjusted Dose**	**Original Intended Dosage**	**Adjusted Dose**
Atazanavir Clarithromycin Darunavir/ Ritonavir[3] Indinavir Itraconazole Ketoconazole Lopinavir/ Ritonavir[3] Nefazodone Nelfinavir Ritonavir Saquinavir Telithromycin Tipranavir/ Ritonavir[3]	Significant increase in colchicine plasma levels[1]; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors.	0.6 mg twice a day 0.6 mg once a day	0.3 mg once a day 0.3 mg once every other day	1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 – 2.4 mg	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Moderate CYP3A4 Inhibitors							
Drug	**Noted or Anticipated Outcome**	**Gout Flares**				**FMF**	
		Prophylaxis of Gout Flares		**Treatment of Gout Flares**			
		Original Intended Dosage	**Adjusted Dose**	**Original Intended Dosage**	**Adjusted Dose**	**Original Intended Dosage**	**Adjusted Dose**
Amprenavir[3] Aprepitant Diltiazem Erythromycin Fluconazole Fosamprenavir[3] (pro-drug of Amprenavir) Grapefruit Juice Verapamil	Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions.	0.6 mg twice a day 0.6 mg once a day	0.3 mg twice a day or 0.6 mg once a day 0.3 mg once a day	1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 – 2.4 mg.	Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day)

36. The Colcrys® labeling provides dose adjustments for colchicine when coadministered with ketoconazole, verapamil, ritonavir, clarithromycin, and other drugs. These dose adjustments are disclosed and claimed in Takeda's Patents. For example, claim 1 of the '298 patent recites the following:

> 1. A method of using colchicine for the treatment of Familial Mediterranean Fever in a human adult or child> 12 years of age in need of treatment thereof, said method comprising:
>
> orally administering a reduced colchicine dosage amount to the human adult or child > 12 years of age in need of treatment for Familial Mediterranean Fever who is concomitantly receiving administration of clarithromycin within 1 to 2 days of oral administration of colchicine, wherein the reduced colchicine dosage amount is reduced compared to a daily dosage amount to be administered in the absence of concomitant clarithromycin,
>
> wherein the daily dosage amount to be administered in the absence of concomitant clarithromycin is a maximum of 2.4 mg per day, and
>
> wherein the reduced colchicine dosage amount is a maximum of 0.6 mg per day.

See Ex. E, claim 1. The dose adjustment table in the Colcrys® labeling provides that the usual intended dose of colchicine for FMF is a maximum of 2.4 mg. When colchicine is used with a strong CYP3A4 inhibitor such as clarithromycin, the Colcrys® labeling teaches that it should be adjusted from 2.4 mg per day to a reduced colchicine dosage of 0.6 mg per day (which may be given as 0.3 mg twice per day).

37. Accordingly, on information and belief, Granules's labeling for its ANDA Product, like the labeling for Colcrys®, recites methods of using colchicine disclosed and claimed in the FMF Patents.

38. If Granules's ANDA Product is approved by the FDA, Granules will induce others to infringe one or more claims of the FMF Patents. Specifically, Granules's label will explicitly instruct doctors, pharmacists, other healthcare professionals, and patients to administer Granules's ANDA Product according to methods claimed in one or more claims of the FMF Patents.

39. On information and belief, Granules's label demonstrates Granules's specific intent that, when concomitant administration is necessary or desirable, a doctor, pharmacist, other healthcare professional, or patient administer Granules's ANDA Product according to the instructions on Granules's labeling regarding dose reduction during concomitant administration and thus directly infringe one or more of claims of the FMF Patents.

40. On information and belief, some FMF patients will undergo concomitant treatment with colchicine for FMF and ketoconazole for a fungal infection.

41. On information and belief, some FMF patients will undergo concomitant treatment with colchicine for FMF and ritonavir for HIV or other viral infections.

42. On information and belief, some FMF patients will undergo concomitant treatment with colchicine for FMF and clarithromycin for bacterial infections, including *H. pylori*.

43. On information and belief, patients concomitantly taking ketoconazole, ritonavir, and/or clarithromycin with colchicine will be prescribed Granules's ANDA Product according to the instructions on Granules's labeling regarding dose reductions in accordance with Takeda's FMF Patents by doctors or other healthcare professionals. Such doctors, healthcare professionals, and patients thus will directly infringe one or more of claims of the FMF Patents.

EXCEPTIONAL CASE

44. On information and belief, Granules is aware of the FMF Patents.

45. Granules had no basis for submitting ANDA No. 210425 or a Paragraph IV Certification. Granules's actions render this an exceptional case under 35 U.S.C. § 285.

COUNT I

(Infringement of the '519 Patent)

46. Paragraphs 1 to 45 are incorporated herein as set forth above.

47. Granules has committed an act of infringement of the '519 Patent that creates a justiciable case or controversy between Takeda and Granules.

48. Granules's submission of its ANDA No. 210425 to seek approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of Granules's ANDA Product to treat FMF prior to expiration of the '519 Patent constitutes infringement of claim 1 of the '519 Patent under 35 U.S.C. § 271(e)(2)(A).

49. Unless enjoined by the Court, upon FDA approval of ANDA No. 210425, Granules will induce infringement of the '519 Patent under 35 U.S.C. § 271(b) by making, using, importing, selling, and offering to sell Granules's ANDA Product in the United States. On information and belief, upon approval of ANDA No. 210425, Granules will intentionally encourage acts of direct infringement by healthcare providers administering, and/or patients using, Granules's ANDA Product with knowledge of the '519 Patent and knowledge that its acts are encouraging infringement.

50. Takeda will be irreparably harmed by Granules's infringing activities unless those activities are enjoined by this Court.

51. Takeda does not have an adequate remedy at law.

COUNT II

(Infringement of the '731 Patent)

52. Paragraphs 1 to 51 are incorporated herein as set forth above.

53. Granules has committed an act of infringement of the ’731 Patent that creates a justiciable case or controversy between Takeda and Granules.

54. Granules’s submission of its ANDA No. 210425 to seek approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of Granules’s ANDA Product to treat FMF prior to expiration of the ’731 Patent constitutes infringement of claim 1 of the ’731 Patent under 35 U.S.C. § 271(e)(2)(A).

55. Unless enjoined by the Court, upon FDA approval of ANDA No. 210425, Granules will induce infringement of the ’731 Patent under 35 U.S.C. § 271(b) by making, using, importing, selling, and offering to sell Granules’s ANDA Product in the United States. On information and belief, upon approval of ANDA No. 210425, Granules will intentionally encourage acts of direct infringement by healthcare providers administering, and/or patients using, Granules’s ANDA Product with knowledge of the ’731 Patent and knowledge that its acts are encouraging infringement.

56. Takeda will be irreparably harmed by Granules’s infringing activities unless those activities are enjoined by this Court.

57. Takeda does not have an adequate remedy at law.

COUNT III

(Infringement of the ’298 Patent)

58. Paragraphs 1 to 57 are incorporated herein as set forth above.

59. Granules has committed an act of infringement of the ’298 Patent that creates a justiciable case or controversy between Takeda and Granules.

60. Granules’s submission of its ANDA No. 210425 to seek approval to engage in the

commercial use, manufacture, sale, offer for sale, or importation of Granules's ANDA Product to treat FMF prior to expiration of the '298 Patent constitutes infringement of one or more claims of the '298 Patent, including at least claim 1 of the '298 Patent, under 35 U.S.C. § 271(e)(2)(A).

61. Unless enjoined by the Court, upon FDA approval of ANDA No. 210425, Granules will induce infringement of the '298 Patent under 35 U.S.C. § 271(b) by making, using, importing, selling, and offering to sell Granules's ANDA Product in the United States. On information and belief, upon approval of ANDA No. 210425, Granules will intentionally encourage acts of direct infringement by healthcare providers administering, and/or patients using, Granules's ANDA Product with knowledge of the '298 Patent and knowledge that its acts are encouraging infringement.

62. Takeda will be irreparably harmed by Granules's infringing activities unless those activities are enjoined by this Court.

63. Takeda does not have an adequate remedy at law.

COUNT IV

(Infringement of the '648 Patent)

64. Paragraphs 1 to 63 are incorporated herein as set forth above.

65. Granules has committed an act of infringement of the '648 Patent that creates a justiciable case or controversy between Takeda and Granules.

66. Granules's submission of its ANDA No. 210425 to seek approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of Granules's ANDA Product to treat FMF prior to expiration of the '648 Patent constitutes infringement of one or more claims of the '648 Patent, including at least claim 1 of the '648 Patent, under 35 U.S.C. § 271(e)(2)(A).

67. Unless enjoined by the Court, upon FDA approval of ANDA No. 210425, Granules will induce infringement of the '648 Patent under 35 U.S.C. § 271(b) by making, using,

importing, selling, and offering to sell Granules's ANDA Product in the United States. On information and belief, upon approval of ANDA No. 210425, Granules will intentionally encourage acts of direct infringement by healthcare providers administering, and/or patients using, Granules's ANDA Product for the treatment of FMF with knowledge of the '648 Patent and knowledge that its acts are encouraging infringement.

68. Takeda will be irreparably harmed by Granules's infringing activities unless those activities are enjoined by this Court.

69. Takeda does not have an adequate remedy at law.

COUNT V

(Infringement of the '297 Patent)

70. Paragraphs 1 to 69 are incorporated herein as set forth above.

71. Granules has committed an act of infringement of the '297 Patent that creates a justiciable case or controversy between Takeda and Granules.

72. Granules's submission of its ANDA No. 210425 to seek approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of Granules's ANDA Product to treat FMF prior to expiration of the '297 Patent constitutes infringement of one or more claims of the '297 Patent, including at least claim 1 of the '297 Patent, under 35 U.S.C. § 271(e)(2)(A).

73. Unless enjoined by the Court, upon FDA approval of ANDA No. 210425, Granules will induce infringement of the '297 Patent under 35 U.S.C. § 271(b) by making, using, importing, selling, and offering to sell Granules's ANDA Product in the United States. On information and belief, upon approval of ANDA No. 210425, Granules will intentionally encourage acts of direct infringement by healthcare providers administering, and/or patients using, Granules's ANDA Product for the treatment of FMF with knowledge of the '297 Patent and knowledge that its acts are encouraging infringement.

74. Takeda will be irreparably harmed by Granules's infringing activities unless those activities are enjoined by this Court.

75. Takeda does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Takeda requests entry of judgment in its favor and against Granules as follows:

A. For a judgment and decree that Granules has infringed one or more claims of the FMF Patents (the '519, '731, '298, '648, and '297 Patents) under 35 U.S.C. § 271(e)(2)(A) by submitting its ANDA No. 210425 with a Paragraph IV Certification seeking approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of Granules's ANDA Product to treat FMF prior to the expiration of the FMF Patents;

B. For a declaration that the commercial use, sale, offer for sale, manufacture, and/or importation by Granules of its ANDA Product would infringe one of more claims of the FMF Patents (the '519, '731, '298, '648, and '297 Patents) under 35 U.S.C. § 271(b);

C. For an order preliminarily and permanently enjoining Granules and its affiliates, subsidiaries, directors, employees, agents, representatives, licensees, successors, assigns, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from infringing the FMF Patents;

D. For an order that, if Granules engages in the commercial manufacture, use, importation into the United States, sale, or offer for sale of its ANDA Product before the expiration of the FMF Patents, a judgment be awarded to Takeda for damages resulting from such infringement, together with interest, in an amount to be determined at trial;

E. For an order pursuant to 35 U.S.C. 271(e)(4)(A) that the effective date for approval of ANDA No. 210425, under § 505(j) of the FFDCA (21 U.S.C. § 355(j)), be no earlier than the expiration date of the last of the FMF Patents, including any extensions or adjustments;

F. For an order declaring this an exceptional case under 35 U.S.C. § 285, and awarding to Takeda its reasonable attorneys' fees, costs, and expenses; and

G. For such other and further relief as this Court deems just and proper.

Respectfully submitted,

Date: September 13, 2017

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