

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KOIOS PHARMACEUTICALS LLC

Petitioner

v.

MEDAC GESELLSCHAFT FUER KLINISCHE SPEZIALPRÄPARATE MBH

Patent Owner

IPR2016-01370

Patent No. 8,664,231

Title: Concentrated Methotrexate Solutions

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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 A. Ground 1: *Grint* Anticipates Claims 1, 2, 4-6, 11-13, 17, and 22.3

 1. The testimony of Patent Owner’s own expert, along with that of
 Petitioner’s expert, establishes that *Grint* anticipates.3

 2. Patent Owner’s arguments were refuted by the testimony of its expert,
 Dr. Zizic, and its CEO, Terri Shoemaker.7

 B. Ground 2: Claims 7-10, 14-16, and 19-21 are Obvious In Light of *Grint* in
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Updated List of Exhibits

Exhibit 1001	U.S. 8,664,231 to Heiner Will, titled, "Concentrated Methotrexate Solutions," filed on March 4, 2009, and issued on March 4, 2014 ("the '231 Patent").
Exhibit 1002	Excerpts from File History for U.S. Patent No. 8,664,231.
Exhibit 1003	U.S. 6,544,504 to Paul Grint et al., titled, "Combined Use of Interleukin 10 and Methotrexate for Immunomodulatory Therapy," filed on June 26, 2000, and issued on April 8, 2003 (" <i>Grint</i> ").
Exhibit 1004	Hoekstra et al. (2004) <i>J. Rheumatol.</i> 31(4):645-47 (" <i>Hoekstra</i> ").
Exhibit 1005	Jørgensen et al. (1996) <i>Ann. Pharmacother.</i> 30:729-32 (" <i>Jørgensen</i> ").
Exhibit 1006	Alsufyani et al. (2003) <i>J. Rheumatol.</i> 31:179-82 (" <i>Alsufyani</i> ").
Exhibit 1007	Declaration of Dr. Elena Massarotti, dated June 2, 2016, in support of Medac's Preliminary Response in IPR2016-00649.
Exhibit 1008	Brooks et al. (1990) <i>Arthritis and Rheum.</i> 33(1):91-94 (" <i>Brooks</i> ").
Exhibit 1009	Medac's Preliminary Response in IPR2016-00649, dated June 2, 2016.
Exhibit 1010	Zackheim (1992) <i>J. Am. Acad. of Derm.</i> 23(6) p. 1008 (" <i>Zackheim</i> ").
Exhibit 1011	Müller-Ladner (2010) <i>The Open Rheumatology Journal</i> 4:15-22. (" <i>Müller-Ladner</i> ").
Exhibit 1012	Weinblatt Declaration; Dated June 17, 2014 (" <i>Weinblatt Decl.</i> ").
Exhibit 1013	Gammon Declaration; Dated June 27, 2014 (" <i>Gammon Decl.</i> ").
Exhibit 1014	Pincus et al. (2003) <i>Clin. Exp. Rheumatol.</i> (Suppl. 31):S179-S185 (" <i>Pincus</i> ").
Exhibit 1015	Insulin Administration, <i>Diabetes Care</i> , 26:1 S121-S124 (2003) (" <i>Insulin Admin</i> ").
Exhibit 1016	Complaint in <i>Medac Pharma, Inc. v. Antares Pharma, Inc.</i> , Nos. 1:14-cv-01498-JBS-KMW.
Exhibit 1017	Portion of EPO prosecution for EP Application No. 07 786 239.9 and Certified English Translation of the same.
Exhibit 1018	Weinblatt (1993) "Methotrexate," in <i>Textbook of Rheumatology</i> , 4th Edition, Chapter 47, (Kelley et al., eds. 1993) (" <i>Weinblatt 1993</i> ").
Exhibit 1019	Schiff et al., "Head-to-head, randomized, crossover study of

	oral versus subcutaneous methotrexate in patients with rheumatoid arthritis,” <i>Ann. Rheum. Dis.</i> 0:1-3 (2014) (“ <i>Schiff</i> ”).
Exhibit 1020	Weinblatt (1995) Efficacy of Methotrexate in Rheumatoid Arthritis, <i>Br. J. Rheum.</i> 34(suppl. 2):43-48 (“ <i>Weinblatt 1995</i> ”).
Exhibit 1021	Product Label for the “Methotrexate Sodium for Injection” product by Wyeth, Date of First Authorization August 10, 1959, Date of Supplement Approval January 27, 2004, Obtained from Archive.org as of April 29, 2005 (“ <i>Wyeth</i> ”), and Internet Archive Affidavit.
Exhibit 1022	2003 Ed. of Physician’s Desk Reference for “Methotrexate Sodium for Injection” by Wyeth (“ <i>the PDR for Wyeth</i> ”).
Exhibit 1023	Arthur et al. (2002) A Study of Parenteral Use of Methotrexate in Rheumatic Conditions, <i>J. Clinical Nursing</i> 2002;11:256-63 (“ <i>Arthur</i> ”).
Exhibit 1024	Arthur et al. (2001) Self-Injection of Gold and Methotrexate, <i>J. Rheumatol.</i> 2001;28(1):212 (“ <i>Arthur 2001</i> ”).
Exhibit 1025	Moitra et al. (2005) Caveats to the use of parenteral methotrexate in the treatment of rheumatic disease, <i>Rheumatology</i> 2005;44:256-57 (“ <i>Moitra</i> ”).
Exhibit 1026	Product Label for “Methotrexate For Injection, USP” by Bigmar, Date of First Authorization February 26, 1999, Obtained from Archive.org as of February 16, 2005 (“ <i>Bigmar</i> ”).
Exhibit 1027	Feagan et al. (1995) Methotrexate for the Treatment of Crohn’s Disease, <i>N. Engl. J. Med.</i> 332(5):292-97 (“ <i>Feagan</i> ”).
Exhibit 1028	Furst et al. (1989) Increasing Methotrexate Effect with Increasing Dose in the Treatment of Resistant Rheumatoid Arthritis, <i>J. Rheum.</i> 16(3):313-20 (“ <i>Furst</i> ”).
Exhibit 1029	Giannini et al. (1992) Methotrexate in resistant juvenile rheumatoid arthritis—results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. <i>N. Engl. J. Med.</i> 326(16):1043, 1045, 1048-49 (“ <i>Giannini</i> ”).
Exhibit 1031	FDA Arthritis Advisory Committee.
Exhibit 1032	Results from Body Surface Area Calculator for Medication Doses (“ <i>BSA Calculation</i> ”).
Exhibit 1033	Miller Declaration and Curriculum Vitae (“ <i>Miller Decl.</i> ”).
Exhibit 1034	Schiff Declaration and Curriculum Vitae (“ <i>Schiff Decl.</i> ”).
Exhibit 1035	Noroozi Declaration (“ <i>Noroozi Decl.</i> ”).

Exhibit 1036	Kamholz Declaration.
Exhibit 1037	Second Kamholz Declaration.
Exhibit 1038	Declaration of Kayvan B. Noroozi in Support of Motion for Admission Pro Hac Vice.
Exhibit 1039	Deposition Transcript of Dr. Thomas Zizic, taken August 25, 2017.
Exhibit 1040	Deposition Transcript of Terri Shoemaker, taken August 30, 2017.
Exhibit 1041	Correspondence between counsel for Koios and Medac, beginning April 26, 2017.
Exhibit 1042	Decision of the U.K. High Court in <i>Accord Healthcare Limited v. Medac Gesellschaft für Klinische Spezialpräparate mbH</i> , January 13, 2016.
Exhibit 1043	Practical Law report on the Court of the Hague Decision, published August 31, 2016.
Exhibit 1044	Non-Final Rejection of U.S. Patent Application No. 14/635,542, filed November 14, 2106.
Exhibit 1045	Notice of Abandonment of U.S. Patent Application No. 14/635,542, filed June 6, 2017.

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