UNITED STATES PATENT AND TRAD	EMARK OFFICE
BEFORE THE PATENT TRIAL AND A	 PPEAL BOARD
AMERIGEN PHARMACEUTICALS ARGENTUM PHARMACEUTIC Petitioners,	
v.	
JANSSEN ONCOLOGY, II Patent Owner.	NC.
Case IPR2016-00286 <sup>1</sup> Patent 8,822,438 B2	

DECLARATION OF MATTHEW B. RETTIG, M.D. IN SUPPORT OF JANSSEN ONCOLOGY, INC.'S <u>PATENT OWNER RESPONSE</u>



<sup>&</sup>lt;sup>1</sup> Case IPR2016-01317 has been joined with this proceeding.

### TABLE OF CONTENTS

I.	Introduction 1					
	A.	Engagement				
	B.	Background and Qualifications1				
	C.	Com	Compensation and Prior Testimony			
	D.	Materials Considered				
II.	Legal	Standa	Standards Regarding Patentability			
III.	Technical Background					
	A.	Cont	Control of Prostate Growth and Function by Androgens			
		1.	Prostate growth and function	7		
		2.	Androgen Synthesis	9		
		3.	Clinical Disorders Associated with Under-Production or Over-Proof Steroids and Their Treatment			
	B.	Prostate Cancer and Its Treatment as of August 2006				
		1.	Prevalence, Diagnosis, and Early Stage Treatment	20		
		2.	First Line Hormonal Therapy for Metastatic Prostate Cancer	22		
		3.	Metastatic Castration Resistant Prostate Cancer	22		
	C.	Endpoints for Evaluating Response to Prostate Cancer Treatment				
IV.	The '	438 Pa	438 Patent and its claims			
V.	Clain	n Const	Construction			
VI.	Perso	n of Oı	rdinary Skill in the Art	32		
VII.	The Prior Art Relied On by Petitioners					
	A.	Gerber (Exhibit 1004) 33				
	B.	The Barrie patent (Exhibit 1005)				
	C.	O'Donnell (Exhibit 1003)				
VIII.	Rebu	tal to Dr. Serels's Opinions Concerning Obviousness				



A.		There Was No Scientific Basis in the Prior Art to Add Prednisone to Abiraterone Acetate for Purposes of Glucocorticoid Replacement				
	1.	As of August 2006, a POSA Would Understand that Abiraterone Acetate's Mechanism of Action and Hormonal Side Effects Were Very Different from Ketoconazole				
	2.	As of August 2006, a POSA Would Understand that Abirateron Did Not Cause Clinical Symptoms Associated with Adrenal Surand Resulted in Normal Cortisol Levels				
		a.	O'Donnell teaches that abiraterone acetate did not have any significant effect upon cortisol levels in patients			
		b.	A POSA Would Have Concluded from the Prior Art as a Whole that Abiraterone Acetate did not Cause Any Clinical Symptoms Requiring Glucocorticoid Replacement			
	3.	"Gluc	August 2006, a POSA Would Understand that Gerber's Use of cocorticoid Replacement' with Ketoconazole Did Not Apply to terone Acetate			
	4.	Prosta	August 2006, a POSA Would Not Have Given Glucocorticoids to ate Cancer Patients Unless There Was a Clear Clinical Need Because eir Known Severe Side Effects and their Potential to Fuel the Cancer 51			
B.			To Scientific or Clinical Basis in the Prior Art to Add Prednisone to Acetate to Address Mineralocorticoid Excess			
	1.	Not C	August 2006, a POSA Would Understand that Ketoconazole Did Cause Mineralocorticoid Excess Syndrome or Symptoms of rtension, Hypokalemia, or Fluid Retention			
	2.		August 2006, Nothing in the Prior Art Would Have Suggested to a that Abiraterone Acetate Would Cause Mineralocorticoid Excess 60			
	3.	POSA	if Mineralocorticoid Excess Was Observed, As of August 2006, a Would Understand that It Could Be Managed Without prorticoid Replacement			
C.	Abirat	terone A	o Scientific or Clinical Basis for Believing that the Combination of Acetate and Prednisone Could Be Successful in Achieving the laimed in the '438 Patent			
	1.		August 2006, the Prior Art Did Not Teach that Ketoconazole was			



			Prior Art Did Not Provide a Scientific or Clinical Basis for Beli Prednisone Would be Effective for Treating Cancer	_	
IX.		Real World Facts Or "Objective Indicia of Non-Obviousness" Support the Non-Obviousness of the '438 Patent Invention			
	A.		n Claimed in the '438 Patent Resulted in Unexpected Clinical	71	
	B.		n Claimed in the '438 Patent is Embodied in ZYTIGA® Theraging Significantly to the Success of ZYTIGA®		
C.		Long Felt Bu	ut Unsolved Need	80	
	D.	Skepticism a	nd Failure of Others	80	
		1. The C	D'Donnell Studies	81	
		2 Other	r Failed Phase III Clinical Trials	82	



I, Matthew B. Rettig, M.D., hereby declare as follows:

#### I. INTRODUCTION

### A. Engagement

1. I have been retained by counsel for Patent Owner Janssen Oncology Inc. ("Janssen") to provide expert and testimony as background for the panel of Administrative Patent Judges of the Patent Trial and Appeal Board of the United States Patent and Trademark Office ("Panel") as it considers issues relating to the patentability of U.S. Patent No. 8,822,438 (the '438 Patent) (Ex. 1001) in an *inter partes review* requested by Amerigen Pharmaceuticals Ltd. and Argentum Pharmaceuticals LLC (collectively "Petitioners") in Case No. IPR2016-00286 and Case No. IPR2016-01317.

## **B.** Background and Qualifications

2. I am Medical Director of the Prostate Cancer Program of the Institute of Urologic Oncology at the David Geffen School of Medicine at the University of California, Los Angeles ("UCLA School of Medicine"). I am also Professor in the Department of Medicine and the Department of Urology at the UCLA School of Medicine. I am also Chief of the Division of Hematology-Oncology for the Veteran's Administration (VA) Greater Los Angeles Healthcare System in West Lost Angeles. In addition, I serve as the Director of the Operation Mend Project to Enhance Cancer Care for Veterans, a collaboration between UCLA and the VA Greater Los Angeles Healthcare System to enhance cancer care for veterans.



# DOCKET

# Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## **Real-Time Litigation Alerts**



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## **Advanced Docket Research**



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## **Analytics At Your Fingertips**



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

#### API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

#### **LAW FIRMS**

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

#### **FINANCIAL INSTITUTIONS**

Litigation and bankruptcy checks for companies and debtors.

#### **E-DISCOVERY AND LEGAL VENDORS**

Sync your system to PACER to automate legal marketing.

