

EXHIBIT A



US010844435B1

(12) **United States Patent**
Vijayan

(10) **Patent No.:** **US 10,844,435 B1**
(45) **Date of Patent:** **Nov. 24, 2020**

(54) **METHOD TO TREAT HYPOTENSION USING VASOPRESSIN IN CERTAIN GENOTYPES**

(71) Applicant: **Par Pharmaceutical, Inc.**, Chestnut Ridge, NY (US)

(72) Inventor: **Saji Vijayan**, Chester Springs, PA (US)

(73) Assignee: **PAR PHARMACEUTICAL, INC.**, Chestnut Ridge, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/932,351**

(22) Filed: **Jul. 17, 2020**

(51) **Int. Cl.**
C12Q 1/6883 (2018.01)
A61P 9/02 (2006.01)
A61K 38/095 (2019.01)

(52) **U.S. Cl.**
CPC **C12Q 1/6883** (2013.01); **A61K 38/095** (2019.01); **A61P 9/02** (2018.01); **C12Q 2600/106** (2013.01)

(58) **Field of Classification Search**
CPC ... C12Q 1/6883; C12Q 2600/106; A61P 9/02; A61K 38/095
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

9,375,478	B1 *	6/2016	Kenney	A61K 47/10
9,687,526	B2 *	6/2017	Kenney	A61K 38/22
9,744,209	B2 *	8/2017	Kenney	A61K 47/02
9,744,239	B2 *	8/2017	Kenney	A61K 47/10
9,750,785	B2 *	9/2017	Kenney	G01N 30/88
9,919,026	B2 *	3/2018	Kenney	A61K 31/045
9,937,182	B2 *	4/2018	Grobe	A61K 31/404
9,937,223	B2 *	4/2018	Kenney	A61K 47/02
2009/0298711	A1 *	12/2009	Russell	C12Q 1/6883 506/16
2015/0374698	A1	12/2015	Grobe et al.		
2015/0377876	A1	12/2015	Grobe et al.		
2018/0228806	A1	8/2018	Grobe et al.		

OTHER PUBLICATIONS

Argenziano et al.; "A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement;" *Circulation*; 1997; 96 (9 Suppl); pp. 286-290.
 Choong et al.; "Vasopressin in pediatric shock and cardiac arrest;" *Pediatr Crit Care Med*; 2008; 9; pp. 372-379.
 Holmes et al.; "Science review: Vasopressin and the cardiovascular system part 1-receptor physiology;" *Crit Care*; 2003; 7; pp. 427-434.
 Jochberger et al.; "The vasopressin and copeptin response to infection, severe sepsis, and septic shock;" *Crit Care Med*; 2009; 37; pp. 476-482.

Landry et al.; "The pathogenesis of vasodilatory shock;" *N Engl J Med*; 2001; 345; pp. 588-595.
 Levin et al.; "Association between arginine vasopressin 1a receptor (AVPR1a) promoter region polymorphisms and prepulse inhibition;" *Psychoneuroendocrinology*; 2009; 34(6) p. 901-908.
 Matsumoto et al.; "Characterization of a recombinant soluble form of human placental leucine aminopeptidase/oxytocinase expressed in Chinese hamster ovary cells;" *Eur J Biochem*; 2000; 267(1); pp. 46-52.
 Mekontso-Dessap et al.; "Risk factors for post-cardiopulmonary bypass vasoplegia in patients with preserved left ventricular function;" *Ann Thorac Surg*; 2001; 71(5); pp. 1428-1432.
 Möhring et al.; "Greatly enhanced pressor response to antidiuretic hormone in patients with impaired cardiovascular reflexes due to idiopathic orthostatic hypotension;" *J Cardiovasc Pharmacol*; 1980; 2(4); pp. 367-376.
 Moses et al.; "Urinary and metabolic clearances of arginine vasopressin in normal subjects;" *Am J Physiol*; 1986; 251 (Regulatory Integration Comp. Physiol. 20); pp. R365-R370.
 Nakada et al. "Leucyl/cystinyl aminopeptidase gene variants in septic shock;" *Chest*; 2011; 139(5); pp. 1042-1049.
 Russell J.; "Vasopressin in vasodilatory and septic shock;" *Curr Opin Crit Care*; 2007; 13; pp. 383-391.
 Russell et. al.; "Vasopressin versus Norepinephrine infusion in patients with septic shock;" *N Engl J Med*; 2008; 358 (9) pp. 877-887.
 Vasostrict (vasopressin injection, USP) [package insert]. Par Pharmaceutical Companies, Inc.; Chestnut Ridge (NY); 2019, 2 pages.
 Wallis et al.; "Vasopressin is a physiological substrate for the insulin-regulated aminopeptidase IRAP;" *Am J Physiol Endocrinol Metab*; 2007; 293(4); pp. E1092-E1102 (first published on Aug. 7, 2007).
 Ramirez-Expósito et al.; "A PCR-RFLP method for detection of the LNPEP encoding human insulin-regulated aminopeptidase (IRAP) rs4869317 polymorphism;" *Indian J Med Res.*; Jul. 2016; 144(1); pp. 120-123.
 Kondo et al.; "The clinical course and pathophysiological investigation of adolescent gestational diabetes insipidus: a case report;" *BMC Endocrine Disorders*; Jan. 30, 2018; 18(1):4 (8 pages); doi: 10.1186/s12902-018-0234-6.
 "The Use of Vasopressin for Septic Shock;" date May 6, 2003, accessed online at <http://www.surgicalcriticalcare.net/Guidelines/vasopressin.pdf> on Jul. 3, 2020. (Year: 2003).
 Hajjar et al.; "Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery;" *Anesthesiology*, vol. 126, pp. 85-93. (Year: 2017).
 Anantasis et al.; "Serious Adverse Events Associated with Vasopressin and Norepinephrine Infusion in Septic Shock;" *Critical Care Medicine*, 2014, vol. 42, No. 8, pp. 1812-1820. (Year: 2014).
 Kristensen et al.; "High-throughput methods for detection of genetic variation;" *BioTechniques*; Feb. 2001; 30:318-332.
 Tsuchihashi et al.; "Progress in high throughput SNP genotyping methods;" *The Pharmacogenomics Journal*; (2002) 2; pp. 103-110.
 Edenberg et al.; "Chapter 16: Laboratory methods for high-throughput genotyping;" *Cold Spring Harbor Laboratory Press*; 2009; pp. 183-193.

(Continued)

Primary Examiner — Marcela M Cordero Garcia
(74) *Attorney, Agent, or Firm* — Mayer Brown LLP

(57) **ABSTRACT**

The present disclosure relates to a method of treating a patient experiencing hypotension, comprising genotyping for a TT, AA, or AT genotype, and administering a therapeutically effective amount of vasopressin based on genotype to maintain a target blood pressure.

US 10,844,435 B1

Page 2

(56)

References Cited

OTHER PUBLICATIONS

Young et al.; "Deconstructing the sources of genotype-phenotype associations in humans;" Science; Sep. 27, 2019; 365(6460); pp. 1396-1400 (Author Manuscript; 18 pages).

Moses et al.; "Effects of Sodium Intake, Furosemide, and Infusion of Atrial Natriuretic Peptide on the Urinary and Metabolic Clearances of Arginine Vasopressin in Normal Subjects;" J Clin Endocrinol Metab; 1990; 70: 222-229.

Varpula et al.; "Hemodynamic variables related to outcome in septic shock;" Intensive Care Med (2005) 31:1066-1071.

Moman et al.; "Impact of individualized target mean arterial pressure for septic shock resuscitation on the incidence of acute kidney injury: a retrospective cohort study;" Ann. Intensive Care (2018) 8:124 (10 pages).

* cited by examiner

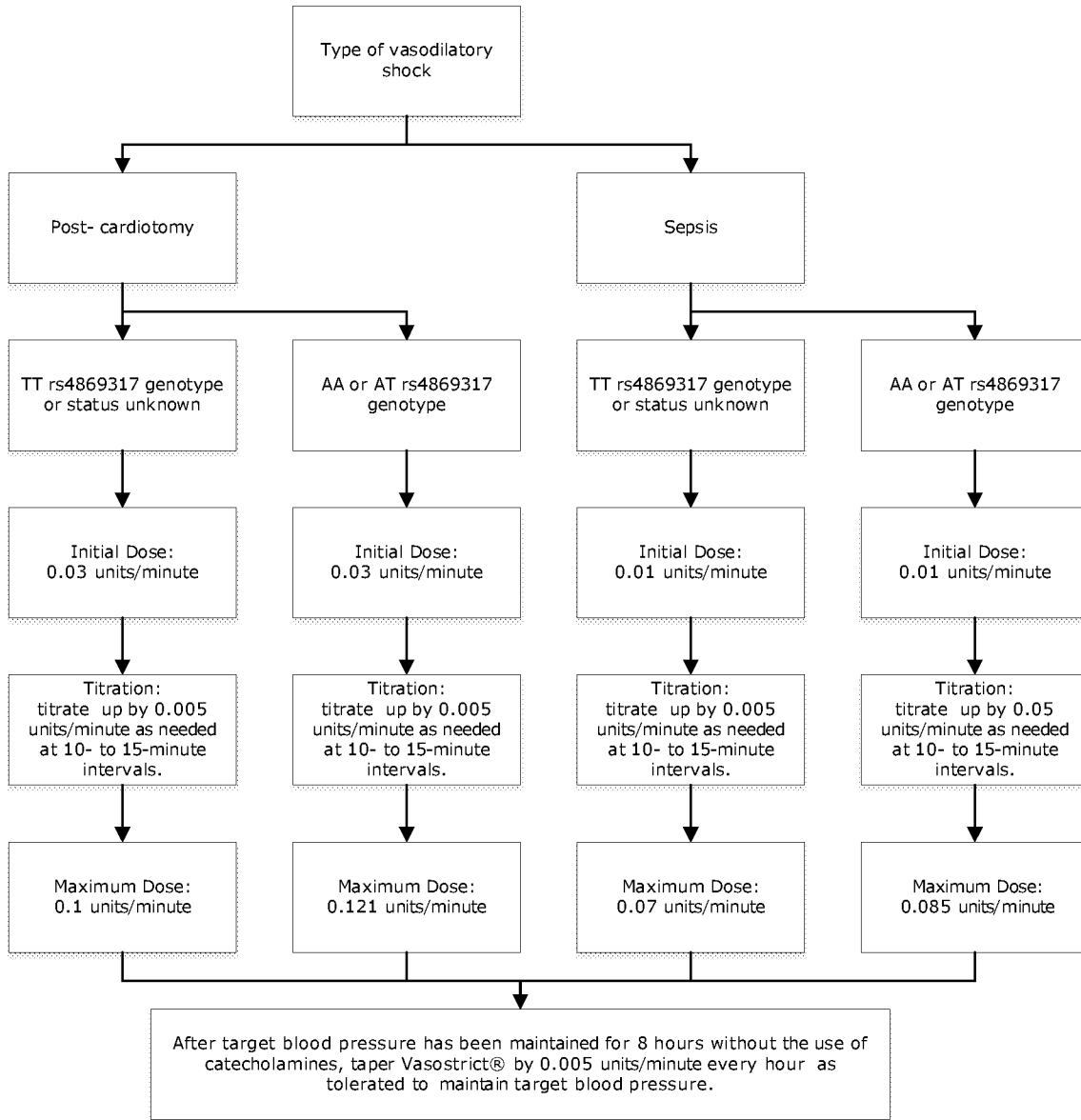


Figure 1

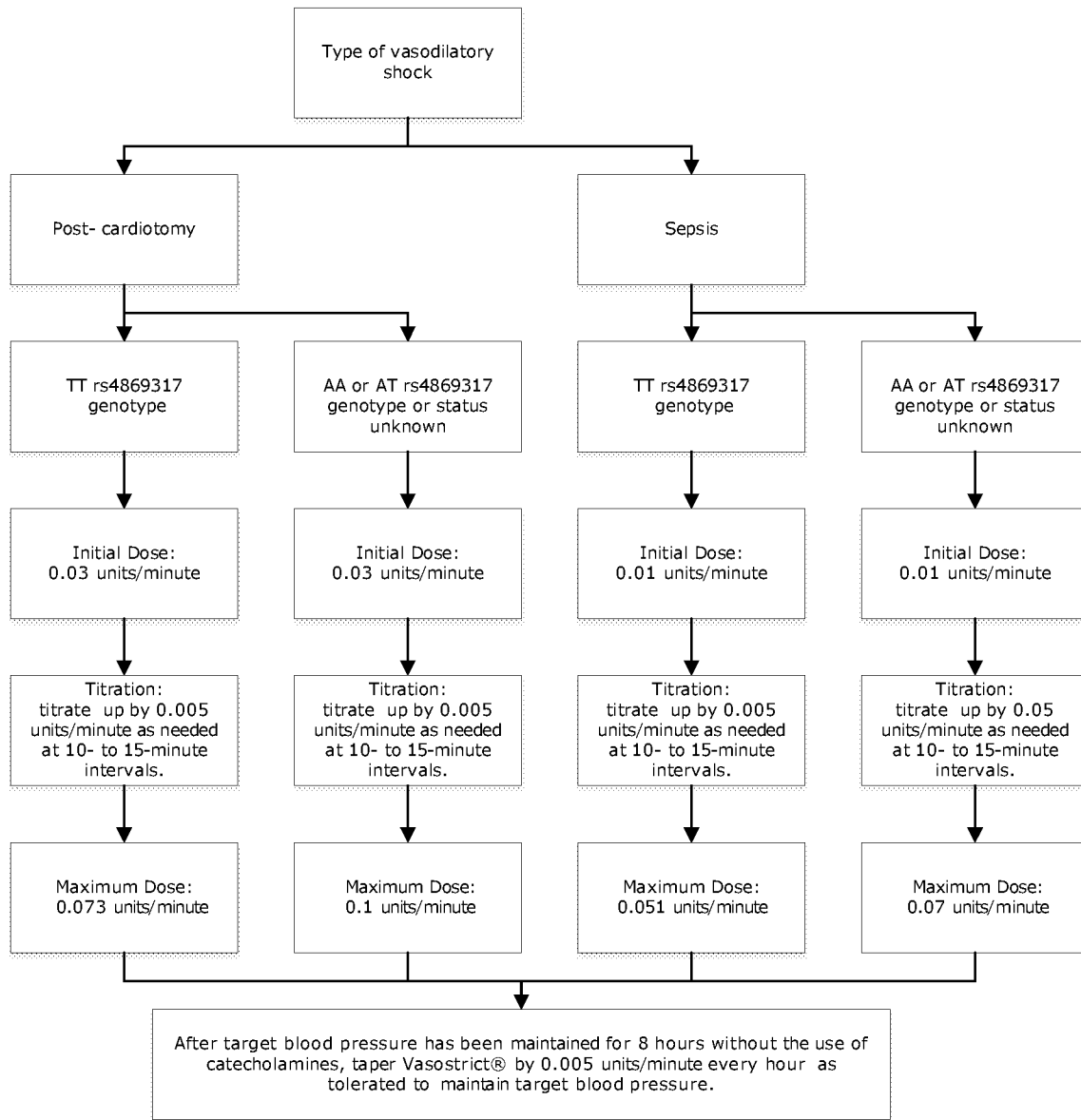


Figure 2

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.