US008399445B2

(12) **United States Patent**
**Pavliv**

(10) **Patent No.: US 8,399,445 B2**
(45) **Date of Patent: Mar. 19, 2013**

(54) **ACETYLCYSTEINE COMPOSITION AND USES THEREOF**

(75) Inventor: **Leo Pavliv**, Cary, NC (US)
(73) Assignee: **Cumberland Pharmaceuticals, Inc.**, Nashville, TN (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.: **13/406,175**
(22) Filed: **Feb. 27, 2012**
(65) **Prior Publication Data**
US 2012/0309832 A1 Dec. 6, 2012

**Related U.S. Application Data**
(62) Division of application No. 11/209,804, filed on Aug. 24, 2005, now Pat. No. 8,148,356.

(51) **Int. Cl.**
*A61K 31/33* (2006.01)
(52) **U.S. Cl.** ..... **514/183**
(58) **Field of Classification Search** ..... 514/183
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 4,849,452 | A | 7/1989 | Dulce et al. |
| 5,114,974 | A | 5/1992 | Rubin |
| 5,124,351 | A | 6/1992 | Rabinovitz et al. |
| 5,206,269 | A | 4/1993 | Ludwig et al. |
| 5,272,166 | A | 12/1993 | Breslow et al. |
| 5,354,748 | A | 10/1994 | Sugita et al. |
| 5,441,748 | A | 8/1995 | Moyiyasu |
| 5,474,757 | A | 12/1995 | Yang |
| 5,691,380 | A | 11/1997 | Mason et al. |
| 5,700,653 | A | 12/1997 | Lu et al. |
| 5,807,894 | A | 9/1998 | Stroppolo et al. |
| 5,882,688 | A | 3/1999 | Alonso et al. |
| 6,103,748 | A | 8/2000 | Bryan |
| 6,114,387 | A | 9/2000 | Cutler |
| 6,149,891 | A | 11/2000 | Korenstein et al. |
| 6,281,222 | B1 | 8/2001 | Salzman et al. |
| 6,355,682 | B1 | 3/2002 | Weinberg |
| 6,468,965 | B1 | 10/2002 | Cutler |
| 6,566,401 | B2 | 5/2003 | Herzenberg et al. |
| 2001/0031737 | A1 | 10/2001 | Richardson et al. |
| 2002/0002146 | A1 | 1/2002 | Halevie-Goldman |
| 2002/0025310 | A1 | 2/2002 | Bland |
| 2002/0031513 | A1 | 3/2002 | Leibovitz |
| 2003/0176359 | A1 | 9/2003 | Neuwelt et al. |
| 2004/0022873 | A1 | 2/2004 | Guilford et al. |
| 2007/0049640 | A1 | 3/2007 | Pavliv |

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| AU | 2006282030 | 3/2008 |
| AU | 2011202871 | 6/2011 |
| CA | 821525 | 8/1969 |
| CA | 2526208 | 12/2004 |
| CA | 2619441 | 2/2008 |
| CN | 200680030443.9 | 2/2008 |
| CN | 201110165261.5 | 6/2011 |
| EP | 0639375 | 2/1995 |
| EP | 2006771456 | 11/2008 |
| FR | 2788436 | 7/2000 |
| GR | 1002731 | 7/1997 |
| HK | 08113428.7 | 12/2008 |
| JP | 7309746 | 11/1995 |
| JP | 2008527905 | 2/2008 |
| KR | 10-2008-7006611 | 3/2008 |
| NZ | 566100 | 2/2008 |
| NZ | 591574 | 3/2011 |
| PH | 12008500349 | 2/2008 |
| SG | 200801568-7 | 2/2008 |
| SG | 201006138-0 | 8/2010 |
| VN | 2008-00711 | 3/2008 |
| VN | 1-2011-03099 | 11/2011 |
| WO | WO0180832 | 11/2001 |
| WO | WO03011249 | 2/2003 |
| WO | WO2007024311 | 3/2007 |

OTHER PUBLICATIONS

Parry, "Effect of N-acetylcysteine on antibiotic activity and bacterial growth in vitro," Journal of Clinical Microbiology, 1977, 5(1): 58-61.
van Laar, "The role of EDTA in provoking allergic reactions to subcutaneous infusion of apomorphine in patients with Parkinson's disease: a histologic study," Movement Disorders, 1998, 13(1):52-55.
Acetadote® (Acetylcysteine) Injection Package Insert (NDA 21-539/S-004).
March, Advanced Organic Chemistry; Reactions, Mechanisms, and Structure, Wiley Interscience, 3rd Ed., 1985, p. 1092.
Dribben, W.H., et al., "Stability and Microbiology of Inhalant NAcetylcysteine Used as an Intravenous Solution for the Treatment of Acetaminophen Poisoning," Ann Emerg. Med., 2003, 42:9-13.
FDA, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products" (2003).
"Airbron," DTB 1966 4: 4.
Rock, "Citizen Petition" (May 18, 2012).
Center for Drug Evaluation and Research, "Chemistry Review NDA 21-539 Acetadote (Acetylcysteine) Injection," Jan. 9, 2003.
Ahola T, Fellman V, Laaksonen R, et al. Pharmacokinetics of intravenous Nacetylcysteine in pre-term new-born infants. Eur J Clin Pham 1999;55:645-50.
Beckett GJ, Donovan JW, Hussey AJ, Proudfoot AT, Prescott LF. Intravenous Nacetylcysteine, hepatotoxicity and plasma glutathione S-transferase in patients with paracetamol overdosage. Hum Exp Toxicol 1990;9(.3): 183-6.
Boesgaard S, Iverson HK, Wroblewski H, et al. Altered peripheral vasodilator profile of nitroglycerin during long-term infusion of N-acetylcysteine. J Amer College Cardio 1994;23:163-9.
Bergstrom L, Kagedal B, Paulsen O. Pharmacokinetics of N-acetylcysteine in man. Eur J Clin Pharmacol 1986:31 (2):217-22.
Bergstrom L, Kagedal B. Dose dependent pharmacokinetics of N-acetylcysteine after oral dosing to man. Biopharm Drug Dispos 1990;11:131-36.
DeCaro L, Ghizzi A, Costa R, et al. Pharmacokinetics and Bioavailability of oral acetylcysteine in healthy volunteers. Arzneimittel forsching 1989;39:382-6.

(Continued)

*Primary Examiner* — Brandon Fetterolf
*Assistant Examiner* — Christopher R Stone
(74) *Attorney, Agent, or Firm* — Stites & Harbison PLLC; Richard S. Myers, Jr.

(57) **ABSTRACT**

This invention relates to novel acetylcysteine compositions in solution, comprising acetylcysteine and which are substantially free of metal chelating agents, such as EDTA. Further, this invention relates to methods of making and using the acetylcysteine compositions. The present compositions and methods are designed to improve patient tolerance and compliance, while at the same time maintaining the stability of the pharmaceutical formulation. The compositions and methods of this invention are useful in the treatment of acetaminophen overdose, acute liver failure, various cancers, methacrylonitrile poisoning, reperfusion injury during cardio bypass surgery, and radiocontrast-induced nephropathy, and can also be used as a mucolytic agent.

**16 Claims, No Drawings**