**IN THE UNITED STATES DISTRICT COURT**
**FOR THE EASTERN DISTRICT OF PENNSYLVANIA**

| | | |
|---|---|---|
| MALLINCKRODT IP, MALLINCKRODT HOSPITAL PRODUCTS INC., and SCR PHARMATOP | ) | |
| Plaintiffs, | ) | C.A. No. ____ |
| v. | ) | |
| B. BRAUN MEDICAL INC. | ) | **COMPLAINT FOR PATENT INFRINGEMENT** |
| Defendant. | ) | |

**COMPLAINT FOR PATENT INFRINGEMENT**

Plaintiffs Mallinckrodt IP, Mallinckrodt Hospital Products Inc., and SCR Pharmatop ("Plaintiffs") for their Complaint against defendant B. Braun Medical Inc. ("Braun"), allege as follows:

**PARTIES**

1. Plaintiff Mallinckrodt IP is a company organized and existing under the laws of Ireland, having a registered address of Damastown Industrial Estate, Mulhaddart, Dublin 15, Ireland. Mallinckrodt IP is a wholly-owned subsidiary of Mallinckrodt plc. As set forth herein, Mallinckrodt IP is the assignee of U.S. Patent No. 9,399,012 ("the '012 patent") and is the exclusive sub-licensee of U.S. Patent No. 6,992,218 ("the '218 patent") (collectively, the "patents-in-suit").

2. Plaintiff Mallinckrodt Hospital Products Inc. ("Mallinckrodt Hospital Products"), formerly Cadence Pharmaceuticals, Inc. ("Cadence"), is a company organized and existing under the laws of Delaware, having a principal place of business at 675 McDonnell Blvd., St. Louis, Missouri 63042. Mallinckrodt Hospital Products is a wholly-owned subsidiary of Mallinckrodt

plc.

3. Plaintiff SCR Pharmatop ("Pharmatop") is a business entity organized and existing under the laws of France, having its headquarters at 10, Square St. Florentin, 78150 Le Chesnay, France. As set forth herein, Pharmatop is the assignee of the '218 patent.

4. Upon information and belief, Defendant Braun is a company organized under the laws of Pennsylvania, having a principal place of business at 824 Twelfth Avenue, Bethlehem, Pennsylvania 18018. Upon information and belief, Braun is in the business of manufacturing, distributing, and selling pharmaceutical products throughout the United States, including in this judicial district.

## NATURE OF THE ACTION

5. This is a civil action for infringement of the patents-in-suit pursuant to the Patent Laws of the United States, 35 U.S.C. §§ 100 *et seq.*; the Federal Food, Drug, and Cosmetic Act; and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 *et seq.*

## JURISDICTION AND VENUE

6. This Court has subject matter jurisdiction over this action under 28 U.S.C. §§ 1331, 1338(a), and 2201(a).

7. This Court has personal jurisdiction over Braun because, upon information and belief, *inter alia*, Braun is Pennsylvania company and has a principal place of business in this District. This Court has personal jurisdiction over Braun for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

8. This Court has personal jurisdiction over Braun because, *inter alia*, Braun has purposefully availed itself of the rights and benefits of Pennsylvania law by engaging in systematic and continuous contacts with Pennsylvania.

9. Upon information and belief, Braun regularly and continuously transacts business

within the Commonwealth of Pennsylvania, including by selling pharmaceutical products in Pennsylvania. Upon information and belief, Braun derives substantial revenue from the sale of those products in Pennsylvania and has availed itself of the privilege of conducting business within the Commonwealth of Pennsylvania.

10. On information and belief, Braun has purposefully availed itself of the benefits of this district by filing patent-related complaints in this district. *See B. Braun Med. Inc. v. Injectimed, Inc.*, 02-cv-09362; *B. Braun Med. Inc. v. Johnson & Johnson*, No. 00-cv-00380; *B. Braun Med. Inc. v. Becton, Dickinson & Co.*, No. 00-cv-00141.

11. This court has personal jurisdiction over Braun because, *inter alia*, upon information and belief, Braun has submitted New Drug Application ("NDA") No. 204957, claiming bioequivalence to Plaintiffs' OFIRMEV® injectable acetaminophen product and seeking nationwide approval of its proposed product. Braun's submission of NDA No. 204957 constitutes infringement of the patents-in-suit pursuant to 35 U.S.C. § 271(e). Braun's tortious act of infringing the patents-in-suit causes concrete harm to Plaintiffs in the Commonwealth of Pennsylvania.

12. Venue is proper in this Court pursuant to 28 U.S.C. § 1391 and 28 U.S.C. § 1400(b).

## THE PATENTS-IN-SUIT

13. The '218 patent, titled "Method for Obtaining Aqueous Formulations of Oxidation-Sensitive Active Principles," was duly and legally issued by the United States Patent and Trademark Office ("PTO") on January 31, 2006. The named inventors assigned the application which issued as the '218 patent to Pharmatop.

14. Pharmatop granted an exclusive license to the '218 patent to Bristol-Myers Squibb Company ("BMS") with a right to sublicense. BMS granted Cadence (now Mallinckrodt

Hospital Products) a sublicense, which was exclusive even to BMS, to the '218 patent with regard to all rights pertinent hereto. As a result of the corporate restructuring following the purchase of Cadence by Mallinckrodt plc, Mallinckrodt IP is the exclusive sub-licensee of the '218 patent. A true and correct copy of the '218 patent is attached as Exhibit A.

15. The '012 patent, titled "Reduced Dose Intravenous Acetaminophen," was duly and legally issued by the PTO on July 26, 2016. The named inventors assigned the application that issued as the '012 patent to Cadence, which subsequently assigned that application to Mallinckrodt IP. Mallinckrodt IP is now the sole assignee of the '012 patent. A true and correct copy of the '012 patent is attached as Exhibit B.

**OFIRMEV®**

16. Cadence obtained approval from the Food and Drug Administration (the "FDA") for NDA No. 022450 for OFIRMEV®, the first and only intravenous (IV) formulation of acetaminophen available in the United States. As part of the corporate restructuring resulting from the purchase of Cadence by Mallinckrodt plc, Mallinckrodt IP is now the holder of NDA No. 022450.

17. OFIRMEV® was approved by the FDA on November 2, 2010. OFIRMEV® is indicated for the treatment of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever.

18. The publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") identifies drug products approved on the basis of safety and effectiveness by the FDA under the Federal Food, Drug, and Cosmetic Act. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '218 and '012 patents were timely listed in the Orange Book with respect to OFIRMEV®.

**DEFENDANT'S INFRINGEMENT OF THE PATENTS-IN-SUIT**

19. Upon information and belief, Braun submitted NDA No. 204957 to the FDA under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)), seeking approval to engage in the commercial manufacture, use, sale or offer for sale, and/or importation of Braun's Generic Product, prior to the expiration of the '218 and '012 patents, both of which are listed in the Orange Book with respect to OFIRMEV®.

20. In the Braun Letter, Braun stated that it had submitted NDA No. 204957 seeking approval to engage in the commercial manufacture, use, sale or offer for sale, and/or importation of Braun's Generic Product prior to the expiration of the '218 patent.

21. The Braun Letter also states that NDA No. 204957 contains a certification under 21 U.S.C. § 355(b)(2)(A)(iv) (the "Paragraph IV certification") alleging that the '218 patent is "invalid, unenforceable and/or will not be infringed by the manufacture, use, or sale of the product for [sic: which] B. Braun's NDA is submitted."

22. Upon information and belief, Braun has taken substantial steps to prepare for the importation, marketing, commercial manufacture, sale and/or offer for sale of Braun's Generic Product.

23. Braun's submission of NDA No. 204957 to the FDA, including its Paragraph IV certification, constitutes infringement of the '218 patent under 35 U.S.C. § 271(e)(2)(A). In the event that Braun commercially manufactures, imports, uses, offers for sale, or sells Braun's Generic Product or induces or contributes to such conduct, said actions would constitute infringement of the '218 patent under 35 U.S.C. § 271(a), (b), and/or (c).

24. Upon information and belief, the only viable way of manufacturing an acetaminophen solution with prolonged stability is to deoxygenate the solution (or the equivalent thereof) to below 2 ppm oxygen. For instance, the proposed generic Exela Pharma Sciences

product was found by this Court to have infringed claims of the '218 patent, and the Cadence product was deemed to be a commercial embodiment thereof. *See Cadence Pharm., Inc. v. Exela Pharma Scis., LLC*, No. 11-733, 2013 WL 11083853 (D. Del. Nov. 14, 2013), *aff'd*, 780 F.3d 1364 (Fed. Cir. 2015)). Wockhardt Bio AG ("Wockhardt") and Agila Specialties Inc. ("Agila") have stipulated to infringement of the '218 patent with regard to their proposed generic versions of OFIRMEV®. BMS; Cadence; Mallinckrodt; Wockhardt; Agila; Paddock Laboratories, Inc.; Fresenius Kabi USA, LLC; and Sandoz, Inc. have taken licenses to the '218 patent. And Perfalgan, the European counterpart of OFIRMEV®, is deoxygenated to below 2 ppm oxygen. *See Cadence*, 2013 WL 11083853, at *5, *33 n.34.

25. Pursuant to 21 U.S.C. §§ 355(b)(2)-(3), because the '012 patent was timely listed in the Orange Book Braun is obligated to provide a patent certification with respect to the '012 patent and to notify Plaintiffs of its certification. Braun stated in the Braun Letter that it had submitted NDA No. 204957 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of Braun's Generic Product prior to the expiration of the '218 patent. Given that Braun acknowledged the existence of the '012 patent in the Braun Letter, and the '012 patent expires after the '218 patent, Braun necessarily is seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of Braun's Generic Product prior to the expiration of the '012 patent. Therefore, upon information and belief, Braun is required to submit a certification under 21 U.S.C. § 355(b)(2)(A)(iv) with regard to the '012 patent.

26. However, Plaintiffs have not received any notification from Braun of a certification with respect to the '012 patent. Pursuant to 35 U.S.C. § 271(e)(2), "[i]t shall be an act of infringement to submit an application under section 505(j) of the Federal Food, Drug, and

Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2). Braun's submission of its NDA seeking approval for Braun's Generic Product is an act of infringement with regard to one or more claims of the Orange Book-listed '012 patent pursuant to 35 U.S.C. § 271(e)(2). *See, e.g.*, *The Meds. Co. v. Eagle Pharm., Inc.*, No. 16-569, 2016 WL 4418230 (D.N.J. Aug. 17, 2016) (holding jurisdiction existed where patents asserted were not listed in Orange Book); *Research Found. of State Univ. of N.Y. v. Mylan Pharm. Inc.*, No. 09-184, 2012 WL 1901267, at *4 (D. Del. May 25, 2012) ("[A] Paragraph IV certification against the [patent] is not required [for a patentee] to bring suit under Section 271(e)(2)").

27. Upon information and belief, the FDA will require the labeling for Braun's Generic Product to be substantially identical to the approved labeling for OFIRMEV®, and Braun's Generic Product, if approved, will be marketed, sold, and/or distributed with labeling that is substantially identical to the labeling for OFIRMEV®.

28. The OFIRMEV® labeling includes instructions for administering OFIRMEV® to treat pain or fever in an adult human or an adolescent human subject weighing at least 50 kg, in need thereof, by administering to the subject, by an intravenous route of administration, a therapeutically effective amount of a pharmaceutical composition comprising 650 mg of acetaminophen and repeating said administration at least once at an interval of 4 hours. A true and correct copy of the OFIRMEV® labeling is attached as Exhibit C.

29. For instance, Section 2.2 of the OFIRMEV® labeling recites that for adults and adolescents weighing 50 kg and over, "the recommended dosage of OFIRMEV is 1000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of OFIRMEV of 1000 mg, a

minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4000 mg per day."

30. Table 1 of the OFIRMEV® labeling also contains recommended dosing information for adults and adolescents weighing 50 kg and over, reciting that the "[d]ose given every 4 hours" is "650 mg."

31. Section 2.4 of the OFIRMEV® labeling provides instructions and/or recommendations for dosing and recites, in pertinent part, that "[f]or doses less than 1000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate container prior to administration. Using aseptic technique, withdraw the appropriate dose (650 mg or weight-based) from an intact sealed OFIRMEV vial and place the measured dose in a separate empty, sterile container (e.g. glass bottle, plastic intravenous container, or syringe) for intravenous infusion . . . ."

32. Section 6.1 of the OFIRMEV® labeling reports on clinical trials in which patients were administered 650 mg OFIRMEV® every 4 hours.

33. Section 14.1 of the OFIRMEV® labeling describes acute pain studies in adults in which patients were administered 650 mg OFIRMEV® every 4 hours. The OFIRMEV® labeling reports that patients receiving OFIRMEV® experienced a statistically significant greater reduction in pain intensity over 24 hours compared to placebo.

34. The OFIRMEV® labeling therefore instructs, recommends, promotes, and/or encourages medical care providers to practice the methods of at least Claims 1 and 39 of the '012 patent.

35. The foregoing information in the OFIRMEV® labeling is essential for the safe and effective use of the drug, particularly given the warnings in the labeling concerning potential

dosing errors. As the warning in the Highlights of Prescribing Information indicates, "[t]ake care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death." The Highlights continue: "Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the recommended maximum daily limits . . . ."

36. As such, on information and belief, the FDA will not allow said information to be excised from a proposed labeling for acetaminophen injection products that allegedly are bioequivalent to OFIRMEV®.

37. Under the Hatch-Waxman Act, the evaluation of infringement involves what the applicant will "likely market if its application is approved." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1248-49 (Fed. Cir. 2000) (citing *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997)).

38. Upon information and belief, the FDA will require the labeling for Braun's Generic Product, if approved, to contain recommendations and/or instructions that are identical or substantially identical to those set forth above from the OFIRMEV® labeling and, therefore, will contain recommendations and/or instructions for treating pain or fever in an adult human or an adolescent human subject weighing at least 50 kg, in need thereof, by administering to the subject, by an intravenous route of administration, a therapeutically effective amount of a pharmaceutical composition comprising 650 mg of acetaminophen and repeating said administration at least once at an interval of 4 hours.

39. Upon information and belief, based on the labeling that is likely to be required by the FDA for Braun's Generic Product, if approved, Braun's Generic Product will be

administered to treat pain or fever in an adult human or an adolescent human subject weighing at least 50 kg, in need thereof, by administering to the subject, by an intravenous route of administration, a therapeutically effective amount of a pharmaceutical composition comprising 650 mg of acetaminophen and repeating said administration at least once at an interval of 4 hours, which administration will constitute direct infringement of at least Claims 1 and 39 of the '012 patent. Upon information and belief, this will occur at Defendant's active behest, and with Defendant's intent, knowledge, and encouragement. Upon information and belief, Defendant will actively induce, encourage, and abet this infringement with knowledge that it is in contravention of Mallinckrodt's rights under the '012 patent.

40. Upon information and belief, Braun's Generic Product is a composition especially made for use in treating pain or fever in an adult human or an adolescent human subject weighing at least 50 kg, in need thereof, by administering to the subject, by an intravenous route of administration, a therapeutically effective amount of a pharmaceutical composition comprising 650 mg of acetaminophen and repeating said administration at least once at an interval of 4 hours, and is not a staple article or commodity of commerce suitable for any substantial noninfringing use.

41. Braun's submission of NDA No. 204957 to the FDA constitutes infringement of the '012 patent under 35 USC § 271(e)(2)(A). Moreover, Braun intends to commercially manufacture, import, use, offer for sale, or sell Braun's Generic Product and/or induce or contribute to such conduct. Said actions would constitute infringement of the '012 patent under 35 USC § 271(a), (b), and/or (c).

42. Upon information and belief, Braun was aware of the patents-in-suit prior to filing NDA No. 204957, and its actions render this an exceptional case under 35 U.S.C. § 285.

43. The acts of infringement by Defendant set forth above will cause Plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless enjoined by this Court.

**COUNT I**
**(Infringement Of The '218 Patent)**

44. Plaintiffs incorporate each of the preceding paragraphs 1 to 43 as if fully set forth herein.

45. Braun's submission of NDA No. 204957, including its Paragraph IV certification, constitutes infringement of the '218 patent by Braun pursuant to 35 U.S.C. § 271(e)(2).

46. Upon information and belief, upon FDA approval of NDA No. 204957, Braun will infringe the '218 patent by making, using, offering to sell, or selling Braun's Generic Product in the United States, and/or importing Braun's Generic Product into the United States, and by actively inducing and/or contributing to infringement by others, in violation of 35 U.S.C. § 271(a), (b), and/or (c).

47. Upon information and belief, Braun had actual and constructive knowledge of the '218 patent prior to filing of NDA No. 204957 and acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '218 patent.

**COUNT II**
**(Declaratory Judgment Of Infringement Of The '218 Patent)**

48. Plaintiffs incorporate each of the preceding paragraphs 1 to 47 as if fully set forth herein.

49. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

50. Plaintiffs are further entitled to a declaration that, if Braun, prior to patent expiry, commercially manufactures, uses, offers for sale, or sells Braun's Generic Product within the

United States, imports Braun's Generic Product into the United States, or induces or contributes to such conduct, Braun would infringe the '218 patent under 35 U.S.C. § 271(a), (b), and/or (c).

51. Plaintiffs are entitled to an injunction restraining and enjoining Defendant and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States of any of Braun's Generic Product until the expiration of the '218 patent, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled.

52. Plaintiffs will be irreparably harmed by Braun's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

**COUNT III**
**(Infringement Of The '012 Patent)**

53. Plaintiffs incorporate each of the preceding paragraphs 1 to 52 as if fully set forth herein.

54. Braun's submission of NDA No. 204957 constitutes infringement of the '012 patent pursuant to 35 U.S.C. § 271(e)(2).

55. Upon information and belief, upon FDA approval of NDA No. 204957, Braun will induce and/or contribute to infringement of at least claims 1 and 39 of the '012 patent by making, using, offering to sell, or selling Braun's Generic Product in the United States, and/or importing Braun's Generic Product into the United States, in violation of 35 U.S.C. § 271.

56. Upon information and belief, upon FDA approval of NDA No. 204957, doctors, nurses, and other medical professionals will directly infringe at least claims 1 and 39 of the '012 patent by using Braun's Generic Product, in violation of 35 U.S.C. § 271(a). Braun's Generic Product will be administered to treat pain or fever in an adult human or an adolescent human

subject weighing at least 50 kg, in need thereof, by administering to the subject, by an intravenous route of administration, a therapeutically effective amount of a pharmaceutical composition comprising 650 mg of acetaminophen and repeating said administration at least once at an interval of 4 hours, which administration will constitute direct infringement of at least Claims 1 and 39 of the '012 patent.

57. Upon information and belief, this direct infringement will occur at Braun's active behest, and with Braun's intent, knowledge, and encouragement. Braun will intentionally encourage infringement of at least Claims 1 and 39 of the '012 patent at least by way of the labeling for Braun's Generic Product which will contain recommendations and/or instructions for treating pain or fever in an adult human or an adolescent human subject weighing at least 50 kg, in need thereof, by administering to the subject, by an intravenous route of administration, a therapeutically effective amount of a pharmaceutical composition comprising 650 mg of acetaminophen and repeating said administration at least once at an interval of 4 hours.

58. Upon information and belief, Braun is aware of the '012 patent, which is listed in the Orange Book with respect to OFIRMEV®, and Braun will actively induce, encourage, and abet this infringement with knowledge that such conduct is in contravention of Mallinckrodt's rights under the '012 patent, in violation of 35 U.S.C. § 271(b).

59. Upon information and belief, Braun's Generic Product is a composition for use in practicing at least Claims 1 and 39 of the '012 patent. Claims 1 and 39 of the '012 patent require administration of intravenous acetaminophen. Braun's Generic Product is intravenous acetaminophen. Accordingly, Braun's Generic Product constitutes a material part of the invention of the '012 patent.

60. Upon information and belief, Defendant is aware of the labeling for OFIRMEV®, which instructs how to use OFIRMEV® to practice the methods of at least Claims 1 and 39 of the '012 patent. Accordingly, upon information and belief, Braun knows that its Generic Product, which is proposed as a generic version of OFIRMEV®, is especially made or especially adapted for use in practicing at least Claims 1 and 39 of the '012 patent and is not a staple article or commodity of commerce suitable for substantial noninfringing use. Braun will intentionally encourage infringement of at least Claims 1 and 39 of the '012 patent at least by way of the labeling for Braun's Generic Product which the FDA likely will require to contain recommendations and/or instructions for treating pain or fever in an adult human or an adolescent human subject weighing at least 50 kg, in need thereof, by administering to the subject, by an intravenous route of administration, a therapeutically effective amount of a pharmaceutical composition comprising 650 mg of acetaminophen and repeating said administration at least once at an interval of 4 hours.

61. Upon information and belief, Braun is aware of the '012 patent, which is listed in the Orange Book with respect to OFIRMEV®, and will contribute to infringement of the '012 patent by offering to sell or selling within the United States or importing into the United States Braun's Generic Product, in violation of 35 U.S.C. § 271(c).

62. Upon information and belief, Braun had actual and constructive knowledge of the application that later issued as the '012 patent prior to filing NDA No. 204957 and acted without a reasonable basis for a good faith belief that they would not be liable for infringing the '012 patent upon its issuance.

## COUNT IV
## (Declaratory Judgment Of Infringement Of The '012 Patent)

63. Plaintiffs incorporate each of the preceding paragraphs 1 to 62 as if fully set forth herein.

64. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

65. The Mallinckrodt Plaintiffs are entitled to a declaration that, if Braun, prior to patent expiry, commercially manufactures, uses, offers for sale, or sells Braun's Generic Product within the United States, imports Braun's Generic Product into the United States, or induces or contributes to such conduct, Braun would infringe the '012 patent under 35 U.S.C. § 271(a), (b) and/or (c).

66. An actual controversy has arisen and now exists between the parties concerning whether Braun will directly or indirectly infringe the '012 patent.

67. The Mallinckrodt Plaintiffs are entitled to an injunction restraining and enjoining Defendant and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States of any of Braun's Generic Product until the expiration of the '012 patent, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled.

68. The Mallinckrodt Plaintiffs will be irreparably harmed by Braun's infringing activities unless those activities are enjoined by this Court. The Mallinckrodt Plaintiffs do not have an adequate remedy at law.

## PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Defendant infringed and is infringing each of the patents-in-suit;

B. An order issued pursuant to 35 U.S.C. § 271(e)(4) that the effective date of any approval of Defendant's NDA No. 204957 shall not be earlier than the expiration date of the patents-in-suit, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled;

C. An order extending the 30-month stay following Plaintiffs' receipt of a notice of certification under 21 U.S.C. § 355(b)(2)(A)(iv) with respect to the '012 patent;

D. A declaration that if Defendant, prior to patent expiry, commercially manufactures, uses, offers for sale, or sells Braun's Generic Product within the United States, imports Braun's Generic Product into the United States, or induces or contributes to such conduct, Defendant would infringe the patents-in-suit;

E. A preliminary and permanent injunction restraining and enjoining Defendant and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States of any of Braun's Generic Product until the expiration of the patents-in-suit, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled;

F. That Plaintiffs be awarded monetary relief if Defendant commercially manufactures, uses, offers for sale, or sells its generic version of Plaintiffs' OFIRMEV® brand product, or any other product that infringes or induces or contributes to the infringement of the patents-in-suit, within the United States before the latest expiration date of the patents-in-suit, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or becomes entitled;

G. A declaration that this is an exceptional case and an award of attorneys' fees pursuant to 35 U.S.C. § 285;

H. An award of costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Dated: April 4, 2017

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# EXHIBIT A

US006992218B2

(12) **United States Patent**
**Dietlin et al.**

(10) **Patent No.: US 6,992,218 B2**
(45) **Date of Patent: Jan. 31, 2006**

(54) **METHOD FOR OBTAINING AQUEOUS FORMULATIONS OF OXIDATION-SENSITIVE ACTIVE PRINCIPLES**

(75) Inventors: **Francois Dietlin**, La Vesinet (FR); **Daniele Fredj**, Gif sur Yvette (FR)

(73) Assignee: **Pharmatop SCR** (FR)

( * ) 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.: **10/332,060**

(22) PCT Filed: **Jun. 6, 2001**

(86) PCT No.: **PCT/FR01/01749**

§ 371 (c)(1),
(2), (4) Date: **Aug. 4, 2003**

(87) PCT Pub. No.: **WO01/93830**

PCT Pub. Date: **Dec. 13, 2001**

(65) **Prior Publication Data**

US 2004/0054012 A1 Mar. 18, 2004

(30) **Foreign Application Priority Data**

Jun. 6, 2000 (FR) ..... 00 07231

(51) **Int. Cl.**
***C07C 209/90*** (2006.01)

(52) **U.S. Cl.** ..... **564/4**; 564/5; 564/6; 564/7; 564/223; 514/617

(58) **Field of Classification Search** ..... 564/4, 564/5, 6, 7, 223; 514/617
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,028,222 A * 2/2000 Dietlin et al. ..... 564/4

* cited by examiner

*Primary Examiner*—Shailendra Kumar
(74) *Attorney, Agent, or Firm*—Charles A. Muserlian

(57) **ABSTRACT**

A method for obtaining aqueous formulations with easily oxidizable active principles, notably phenols, stable over a prolonged period, comprising subjecting them to extreme deoxygenation by bubbling with an inert gas and/or placing wider vaccum, protecting them against possible resorption of oxygen by keeping them under an inert gas atmosphere, by filling, under inert gas, into bottles previously cleared of air by insufflation with inert gas, then subjecting them, while stoppering, to low pressure as obtained in the bottle, of 65,000 Pa maximum, to obtain aqueous solutions having a residual oxygen concentration in the solution below 2 ppm, and preferably of the order of 1 ppm and even 0.5 ppm useful as injectable preparations having an oxygen concentration in the solution below 2 ppm.

**19 Claims, No Drawings**

# METHOD FOR OBTAINING AQUEOUS FORMULATIONS OF OXIDATION-SENSITIVE ACTIVE PRINCIPLES

This application is a 371 of PCT/FR01/01749 filed Jun. 6, 2001.

The object of the present invention is a new method for producing injectable aqueous solutions with active principles, in particular active principles which are useful in therapeutics and susceptible to oxygen, and also a procedure for preparation of these methods of packaging, and their utilization.

Its object is, more precisely, a new method for aqueous formulations with active principles susceptible to oxidation which can notably be utilized in injectable preparations being stable over a long period, and containing, for example, phenolic or polyphenolic substances, amino alcohols or sulphur-containing substances.

Aqueous solutions with active principles traditionally have different applications, notably in therapeutics, in particular in the form of injectable solutions intended for humans or animals. However, it happens that some of these active principles present problems of stability in solution. These problems may be connected with the fact that the active principles are susceptible to oxidation and form undesired degradation products by reaction with the oxygen in the air, or above all with the oxygen dissolved in the aqueous solution. Other active principles are indirectly susceptible to oxygen, i.e. whilst being kept they are likely to form, by chemical reactions, oxidizable derivatives. These derivatives, by reacting with oxygen, then lead to the formation of undesired secondary products. This is the case, in particular, with paracetamol. The Applicants have, in fact, demonstrated the fact that paracetamol, in aqueous solution, undergoes hydrolysis on the one hand, and on the other hand, degrades to form a quinone-imine susceptible to polymerization into nitrogenous polymers. The derivatives resulting from these reactions are themselves also susceptible to oxidation and form undesired secondary products.

The secondary products formed by reaction of the oxygen with these active principles, or their derivatives, leads to numerous disadvantages such as, for example, a loss of activity or the production of allergenic products.

In fact, as a result of degradation by oxidation, the titre of active principle in the aqueous solution is considerably reduced, in an uncontrollable manner, and poses a major problem, especially when these solutions are used in therapeutics, more particularly in the form of injectable solutions, when it is important that the dose of active principle is precisely determined.

Moreover, the oxidation products lead to the formation of coloured compounds, thus making the aqueous solution unsuitable for therapeutic applications.

In addition, the formation of secondary products may further increase as a result of a rise in temperature, which, consequently, may cause heat-sterilization of the aqueous solutions with these active principles, impossible, or at least difficult.

Here and in the following text, the term "phenolic active principle susceptible to oxidation" means any substance, which may or may not be medicinal, comprising a phenolic structure and/or functions supported by the phenolic structure which react easily with oxygen, and which degrades forming oxidation products, coloured or colourless, or hydrolysis products or polymerization products.

The active principles susceptible to oxygen are essentially organic substances bearing oxidizable functions,



amongst which the following may in particular be cited: phenols, polyphenols, aminophenols, phenolic alcohols and phenolic ketones, as well as aromatic amines or partially hydrogenated cyclical structures such as derivatives of anthraquinone. The following ones may also be cited:compounds with an enolic structure or with an aldehyde function, or a ketone function or an alcohol function.

Aminosides which are also susceptible to the presence of oxygen may also be cited.

Amongst the easily oxidizable active principles that will be incorporated into the aqueous solutions of the invention, the following may be cited more particularly: phenols or aminophenols, such as paracetamol, epinephrine, norepinephrine, adrenalone, isoprenaline, orciprenaline, isoxuprine, phenylephrine or dobutamine; the following will be cited as aromatic amines: procaine, bupivacaine, tetracaine, butoform, L-dopa or Carbidopa; the following one will be cited as aminoketones:Propaphenone; the following ones will be cited as aminoglucosides: the gentamycines, amikacine, dibekacine, netilmycin, sisomycin, tobramycin, micronomycine; as phenothiazines, promethazine; as hydroaromatic molecules, riboflavin, 9-amino dihydro acridine; further cortisonic derivatives may be cited, such as dexamethasone, betamethasone, triamcinolone, fluocinonide, flunisolide, fluocinolone acetonide, fluocortolone, Clobetasone and their derivatives, beclometasone and its esters; Tetracycline derivatives, such as Doxycycline or Minocycline.

For the purpose of improving the stability of such medicinal active principles which are susceptible to oxidation, and thus to overcome the disadvantages described above, a proposal has already been made to prevent the action of the oxygen, either by eliminating the oxygen, or by neutralizing it, or again by combining both these types of operation.

Several methods have been used for this purpose:

a) elimination of the oxygen by raising the temperature of the aqueous solution, by putting the aqueous solution under vacuum or by bubbling an inert gas such as nitrogen, carbon dioxide or argon through the solution.

However these methods have the disadvantage of allowing only a partial and insufficient elimination of the oxygen, or requiring a considerable amount of time. The bubbling of nitrogen, the method most practised within the pharmaceuticals industry, only allows the oxygen content to be reduced to values of the order of 2 ppm maximum.

b) neutralization of the oxygen dissolved in the aqueous solution, by the addition to the latter of an antioxidant such as a thiol or sulphur anhydride derivatives such as the sulphites, bisulphites or alkali metal metabisulphites.

c) a combination of the elimination of oxygen and the addition of an antioxidant. A method of this type has been described by the Applicants in the French patent 2.751.875.

All the above methods have a certain efficacy. However, oxygen shows a very great facility to dissolve in water, making it necessary to ensure that the solution, once deoxygenated, does not subsequently come into contact with atmospheric air, otherwise the advantage of having previously eliminated the oxygen will be lost.

Within the framework of the industrial manufacture of injectable solutions, it has been easy to deoxygenate bulk solutions in air-tight tanks and thus to keep them away from the air. However, during subsequent bottle or bag filling and packaging operations, it is difficult to keep the solutions totally away from air. In spite of precautions that may be taken for this purpose, especially filling and packaging the

bottles with the addition of inert gas, once packaged, the solutions can may once again contain, or fix, or take up significant quantities of dissolved oxygen.

If these solutions have to be heat-sterilized, especially at high temperatures in the region of 120° C., the residual quantity of dissolved oxygen can easily react with the active principle susceptible to oxidation, resulting in its total or partial degradation.

In effect it has been found that the presence of any oxygen is harmful and that infinitesimal quantities are sufficient to bring about an oxidation reaction, especially at sterilization temperature. The residual oxygen concentration limit present in the medium, likely to produce an oxidizing effect, is of the order of 2 ppm.

The applicants have thus made use of a method for stabilizing of the solutions of phenolic, easily oxidizable substances, in which deoxygenation has previous been completed to a degree that would avoid the possibility of this degradation occurring.

It is known, moreover, that the utilization of antioxidants is not always purely advantageous. Thus, the antioxidants used gradually degrade, which makes it necessary to add relatively large quantities of them to ensure satisfactory protection of the active principle.

It is also possible to combine the elimination of oxygen with the addition of an antioxidant.

Complementary tests have shown that the problem of stabilization of the formulations according to the invention was appreciably more complex than anticipated, and it has notably been established that, without antioxidant, an essentially deoxygenated solution became pink in colour after a certain time at ambient temperature. In this respect it has been observed that injectable solutions which are not completely deoxygenated do not become appreciably coloured if an α-hydroxypolycarboxylic acid is previously added to the solution, in particular the addition of citric acid, or an alkaline citrate, or a mixture of the two, makes it possible to slow down the appearance of a coloration.

In addition, it has emerged that it is possible to complete the deoxygenation of a solution of a substance susceptible to oxidation by the use of vacuum. This results is a greater stability of the antioxidant and less formation of secondary products resulting from oxidative degradation, notably after several sterilization cycles.

The α-hydroxypolycarboxylic acids and their salts, play an important role. They do not act by stabilizing the pH, nor by playing a role capturing free radicals. They advantageously replace polyhydroxylated compounds such as sorbitol or mannitol.

In the particular case of paracetamol, a mixture of trisodic citrate and citric acid is preferably used, in a quantity sufficient to obtain a pH value of the order of 5 to 6, and preferably 5.5.

The object of the present invention is therefore a procedure for preparation of formulations of aqueous solutions with phenolic active principles, in particular active principles susceptible to oxidation, like paracetamol, making it possible to confer a high degree of stability over the course of time.

A further object of the present invention consists of the utilization of these formulations for the production of injectable aqueous solutions intended for humans or animals, containing an added phenolic active principle to which an anti-inflammatory agent and/or central analgesic may or may not be added.

The object of the invention is specifically a method for producing an aqueous formulations containing easily oxidizable phenolic active principles, which are stable over a long period of time, possibly containing antioxidants, characterized in that they are obtained by submitting them to extreme deoxygenation either by bubbling of an inert gas, or by placing under vacuum, then protecting them from possible resorption of oxygen during the course of production, by keeping them in an inert gas atmosphere, by packaging them into bottles previously cleared of air by insufflation with inert gas, and notably topping gas which is heavier than air, such as argon, then in that, at the moment of stoppering, they are subjected to a reduction in pressure, so that a pressure is obtained, which is lower than atmospheric pressure, of 65,000 Pa maximum, preferably between 5,000 and 50,000 Pa, to obtain an aqueous solution having an oxygen concentration in the solution below 2 ppm.

According to another aspect of the invention, the invention consists of a method for preparing of a formulation as previously described, which includes the following stages:

a) an aqueous solution with at least one active principle is subjected to extreme, and possibly complete, deoxygenation,
b) under an inert gas atmosphere, part or all of the deoxygenated aqueous solution is introduced into a container previously cleared of the air contained therein,
c) the container is stoppered under an inert gas atmosphere, in such a way as to create within the container a maximum pressure of 65,000 Pa.

The aqueous solution is preferably deoxygenated by bubbling through an inert gas, such as nitrogen. The bubbling process can be continued until a content of less than 2 ppm is obtained, preferably a content of 1–0.5 ppm, and particularly even 0.05 ppm of oxygen in the aqueous solution. The deoxygenated solution thus obtained can then be conveyed, safe from the air, into a filling machine, to be distributed into containers such as flasks, ampoules or bottles.

The aqueous solution is introduced into the container under an inert gas atmosphere, such as nitrogen. Before the aqueous solution with active principle is introduced into the container, the latter is cleared of the air contained therein, for example by insufflation of an inert gas, preferably an inert gas heavier than air, such as argon, so that the latter is not immediately replaced by air in accordance with Archimedes' principle.

Once the containers have been filled, with constant insufflation of an inert gas, the bottles are stoppered under an extreme vacuum to keep them, after stoppering, at a pressure of 65,000 Pa or below, preferably between 5,000 et 50,000 Pa. To do this, known means can be utilized, such as placing a vacuum bell-jar over the neck of the container, immediately after the stopper is put in. After being placed in hermetic contact, the inside of the bell-jar is placed under a vacuum, for example by linking it to a container under vacuum. The stopper of the container is raised and the gas rising above the solution is aspirated. The stopper is then replaced in the container and the latter can be hermetically sealed, for example by fitting on a capsule, then crimping. The container, once stoppered, can be subjected to a sterilization process, in particular sterilization by autoclaving or irradiation.

The aqueous solution containing an active principle can be subjected to sterilization by sterilising filtration before this solution is introduced into the container. The solution is then introduced into the container, preferably under aseptic conditions, under an inert gas, the latter advantageously being sterile.

The inert gas preferably used in the method according to the invention for bubbling is nitrogen, that used for topping is argon, which is heavier than air. Xenon or neon can also be used.

After the bottles have been filled, with constant insufflation of an inert gas, with the solution of easily oxidizable substance, the bottle is stoppered under an extreme vacuum, to maintain in the bottles after stoppering, a low pressure of more than 300 mm of mercury, or a maximum pressure of 65,000 Pa.

According to the invention procedure, the low pressure prevailing in the bottle promotes the elimination of the oxygen still present in the solution and this constitutes a distinct advantage.

This elimination makes it possible to reduce the quantity of antioxidant necessary for protection of the active principle, or even avoid adding it. It also allows heat-sterilization of solutions that could not be sterilized previously due to degradation of the active principle and/or antioxidant by oxidation during this operation. This reduction in the quantity of antioxidant may also allow these solutions to be stabilized for longer periods.

Thus, French patent 2.751.875 mentions that aqueous solutions of paracetamol are stable for 48 hours at ambient temperature, under light, and at 70° C. in darkness, if they are subjected to bubbling with nitrogen, filling under nitrogen and the addition of an antioxidant. It is possible to obtain stability of longer duration, by using the procedure described, as shown by the following examples.

The antioxidant that it may be appropriate to add to the medium is a sulphite, or sulphite derivative, a thiolic substance such as, for example, cysteine, acetylcysteine, dithiothreitol or α-thioglycerol, thiomalic acid, thioglycerol, methionine; a hydroxylated substance such as ascorbic acid, iso-ascorbic acid, mannitol, sorbitol, a ethylenically unsaturated substance such as sorbic acid, undecylenic acid or fumaric acid or a hydroxy polycarboxylic acid, or a reducing sugar such as trehalulose, maltulose or isomaltulose.

Moreover, it has been found that the addition of a hydroxypolycarboxylic acid in conjunction with, or instead of the deoxygenation operation, has the effect of appreciably reducing the consumption of antioxidant and leads to a reduction in the concentration of antioxidant. The quantity of antioxidant that it may be appropriate to add is low, preferably ranging from 0,1 mg to 1 000 mg per litre of solution, and preferably from 0,2 to 20 mg.

It may also be advantageous to add a pH regulation agent, and in particular a buffering agent, especially when the easily oxidizable phenolic active principles are susceptible to being degraded or hydrolysed within particular pH ranges. It may thus be appropriate to adjust the pH of the solutions between 4 and 8 and particularly between 4.5 and 6.0 where the oxidizability of the phenolic molecules will be lower. An appropriate buffer will be, for example, a sodium hydrogenophosphate/hydrochloric acid mixture, sodium hydrogenophosphate/sodium hydroxide mixture, disodic phosphate/phosphoric acid mixture, acetic acid/sodium acetate mixture, citric acid/sodium citrate mixture, or trisodic citrate/hydrochloric acid mixture. The choice of pH will depend mainly on the nature of the active principle and its character of oxydizability.

The formulations according to the invention are utilized in the field of therapeutics in injectable form administered directly or added to a perfusion bag as an analgesic or an antibiotic or as a cardio-vascular drug. The injectable solution of paracetamol according to the invention is distinguished by quite remarkable analgesic properties. It may in addition contain a vasoconstrictor such as adrenalin or a central analgesic such as codeine or d-propoxyphene or an anti-inflammatory agent such as tiaprofenic acid or one of its salts.

Preparation of such a solution is carried out under nitrogen. The dissolved oxygen concentration is less than 0.05 ppm.

It is also possible to use as hydroxypolycarboxylic acid, tartaric acid or an alkaline monotartarate such as sodium salt or potassium salt in the presence of a dimetallic tartarate to obtain a pH value of the order of 5.5. It has also been noted that in the presence of hydroxypolycarboxylic acid, the pH is much more stable. The same is true for other hydroxypolycarboxylic acids such as gluconic acid, saccharic acid, citramalic acid or malic acid.

It is also possible only to use a hydroxypolycarboxylic acid salt such as trisodic citrate or disodic tartarate and adjust the pH by the moderate addition of hydrochloric acid.

The addition of hydroxypolycarboxylic acid and notably citric acid, at concentrations that make it possible to obtain a pH value of the order of 5.5, plays an important role. It has been shown that concentrations ranging from 5 to 200 mg per 100 ml ensure effective protection against oxidation (absence of coloration) and protection against degradation of the antioxidant attested by a lower content of degradation products of the cysteine used as an antioxidant.

In particular, in the case of paracetamol, after the addition of trisodic citrate at a concentration of 70 mg/100 ml of solution, the residual cysteine concentration is approximately double than that of preparations without citrate, no coloration appeared, even after 7 weeks at 40° C., and there was no variation in the concentration of paracetamol.

In conclusion, the four parameters that have to be taken into consideration as essential for preservation following heat sterilization of aqueous formulations with an active principle susceptible to oxidation are, taken separately or in combination:

- complete deoxygenation by bubbling with inert gas below an oxygen concentration of less than 2 ppm,
- completed by the possible addition of an antioxidant,
- the addition of a hydroxypolycarboxylic acid,
- and the introduction of the aqueous solutions under an atmosphere of inert gas such as argon into a container from which the air has previously been removed.

Under these conditions, the concentration of active principle does not undergo any variation and the absence of oxidation can be established by maintaining colourless solutions for a prolonged period of time.

## EXAMPLE I

### Production of an Aqueous Compound of Paracetamol

A paracetamol solution is prepared in water at a concentration ranging from 2 to 50 mg/ml. Extreme deoxygenation to less than 2 ppm was carried out by bubbling with inert gas, then placing in bottles under inert gas and under vacuum (less than 65,000 Pa of residual pressure). Thus a residual concentration of oxygen is maintained in the solution, of less than 2 ppm and preferably below 1 ppm.

The pH of the solution is between 4 and 8, and preferably 4.5 to 6.0. For this purpose a buffer system is added, adjusted to 5.5.

The addition of an antioxidant contributes to the stability of the solution. The preferred antioxidants are: ascorbic acid, an ascorbate, a thiol, a polyol or a hydroxypolycarboxylic acid.

The preferred antioxidant is the cysteine sodium citrate mixture.

An isotonizing agent can be added to the solution.

## EXAMPLE II

### Production of an Aqueous Compound of Paracetamol without Antioxidant (Example for Comparison)

A 10 mg/ml aqueous paracetamol solution is prepared. Adjustment to pH 5.5 is carried out by the addition of HCl, and buffering by the addition of sodium hydrogenophosphate.

Deoxygenation is then carried out by bubbling with nitrogen, until a residual oxygen content of approximately 0.2 ppm is obtained. After the bottles are filled with the solution during prolonged bubbling with nitrogen, they are sterilized at 121° C. for 15 minutes.

After being kept at 25° C. for 6 months, the solution is still colourless, there is no change in the paracetamol content, and the content of degradation products of paracetamol determined by HPLC remains lower than 0.015% of the paracetamol.

In another test, the paracetamol solution, after being subjected to bubbling with nitrogen, has been packaged under nitrogen. When the bottles of solution are stoppered, a vacuum is applied, to obtain a residual pressure of less than 10,000 Pa The residual dissolved oxygen content was 0.16 ppm. After sterilization at 121° C. for 15 minutes, and after being kept for 8 days at 30° C., the solution remained colourless.

It thus appears that the essential means is deoxygenation to below a residual concentration of the order of 0.2 ppm and this means makes it possible to obtain complete preservation for a prolonged period. The possible presence of an antioxidant completes the effect of the deoxygenation but does not replace it.

## EXAMPLE III

### Production of an Aqueous Solution of Paracetamol Containing Citrate Ions

It has been established that aqueous solutions of paracetamol containing slightly higher residual concentrations of oxygen, i.e of the order of 0.3 to 0.4 ppm, keep less well due to the fact that the paracetamol can react with very small quantities of oxygen and can form coloured compounds.

Thus a 10 mg/ml paracetamol solution adjusted to pH 5.5 by hydrochloric acid was subjected to bubbling with nitrogen until an oxygen content of approximately 0.4 ppm was obtained. The bottles were sterilized at 121° C. for 15 minutes and kept at ambient temperature. After being kept for 9 days, a yellow-pink coloration was observed in the paracetamol solution.

Conversely, if a stabilizing agent in the form of a mixture of citric acid and sodium citrate is added to a composition identical to the above, adjustment of the pH to 5.5 occurs spontaneously and it is not necessary to add hydrochloric acid. After bubbling with nitrogen, the residual oxygen content is of the order of 0.4 ppm. Afterwards the solution is packaged into bottles under vacuum and sterilized at 121° C. for 15 minutes. The bottles are kept for 67 days at ambient temperature. The solution remains perfectly colourless.

This result is unexpected, as the action of the citrate ion cannot be related either to the antioxidants' complexing properties, nor to their reinforcing properties. Moreover, the particular effect of the citrate ion cannot be related to an antioxidizing action.

## EXAMPLE IV

### Stabilization of Partially Deoxygenated Aqueous Paracetamol Solutions

For greater residual oxygen contents, that may reach 1.5 ppm, it is preferable to resort to the addition of a stabilizing agent with more powerful antioxidant properties such as a sulphite, a thiol derivative or an ascorbate.

A 10 mg/ml aqueous paracetamol solution adjusted to pH 5.5 by sodium hydroxide and buffered at this value by sodium acetate was made isotonic by a sufficient quantity of sodium chloride, then an antioxidant is added to it, in this case 0.20 mg/ml cysteine chlorhydrate. This solution was subjected to bubbling with nitrogen then placed under vacuum (low pressure approx. 550 mm of Hg) before stoppering the bottles. The residual oxygen content amounted to approx. 1.5 ppm of dissolved oxygen. After sterilization, the bottles containing this solution were kept for 24 months at 25° C. The bottles remained colourless after this period, the paracetamol content was 100% of the original value, and the degradation products of the paracetamol measured by HPLC represented less than 0.02% of the paracetamol content.

The presence of an antioxidant thus played an important role. In the paracetamol solution, the antioxidant, like cysteine, reacts with the dissolved oxygen by taking the place of the phenolic molecule that is to be protected.

However, after being kept the cysteine almost completely disappeared and cystine is formed, which is the major oxidation product of cysteine.

## EXAMPLE V

### Buffered and Stabilized Aqueous Paracetamol Solutions

Knowing that citrate ions have a stabilizing effect with regard to paracetamol, it was desirable to check whether this effect could be explained by a protective action vis-à-vis the antioxidant, such as cysteine.

A 0.25 mg/ml aqueous cysteine solution was adjusted to pH 5.5, made isotonic by sodium chloride and buffered using as a buffering agent: dehydrated sodium citrate (0.70 mg/ml), sodium acetate, sodium hydrogenophosphate, in quantities equimolar to that of the citrate.

These solutions which involved neither bubbling with nitrogen, nor being placed under vacuum, contained approx. 7 ppm of dissolved oxygen. They were kept in darkness at 25° C. for 3 days.

The dosages carried out showed that the lowest residual cysteine content is found either in non-buffered solutions (15%), or in the presence of citrate. In contrast, in the presence of acetate (18%) or hydrogenophosphate (21%) it is higher.

It follows that the citrate ions do not have any particular protective effect vis-à-vis an antioxidant such as cysteine.

## EXAMPLE VI

### Preparation of Buffered Paracetamol Solutions

In this test, paracetamol, cysteine and a buffer were brought together. A quantity of sodium citrate (in the form of dihydrated disodic citrate) was added to 10 mg/ml aqueous paracetamol solutions, made isotonic by NaCl and stabilized by the addition of cysteine hydrochlorhide (0.25 mg/ml) suitable for adjusting the pH to 5.5. A quantity of citrate of the order of 0.7 mg/ml is sufficient. Comparative solutions were prepared without sodium citrate or replacing the citrate ions by equimolar quantities to those of the citrate, of either sodium acetate, or sodium hydrogenophosphate; in all cases adjusting the pH to a value of 5.5 by the addition of sodium hydroxide or hydrochloric acid.

The solutions were not subjected to bubbling with inert gas (nitrogen) and were kept in darkness at 25° C. for 3 days.

The presence of residual cysteine is thus established in increasing quantities, in the non-buffered solution (42%), in the presence of sodium acetate (17%), in the presence of sodium hydrogenophosphate (21%) and in the presence of citrate (22%) respectively.

After being kept for 20 days, all the solutions were strongly coloured with the exception of the solution containing citrate ions, which had remained colourless. It is established that in the presence of paracetamol, cysteine is protected by the presence of citrate, whilst in the absence of citrate, the cysteine has no protective effect.

Table 1 below illustrates the conclusions set forth above:

The experiments thus evidence the interactions in the presence of different oxygen contents:

| Solution | Oxygen content | Results |
|---|---|---|
| Paracetamol alone | 0.2 ppm | No degradation of the paracetamol |
| Paracetamol + citrate | 0.4 ppm | No degradation of the paracetamol |
| Paracetamol + cysteine | 1.5 ppm | No degradation of the paracetamol |
| Cysteine + citrate | 7 ppm | No protection of the cysteine |
| Paracetamol + cysteine + citrate | 7 ppm | Protection of paracetamol and cysteine |

Unexpectedly, it was by bringing together paracetamol, cysteine and citrate that the best preserving properties were obtained, both for cysteine and for paracetamol even in the presence of oxygen.

The same tests were repeated with more highly concentrated paracetamol solutions.

| Constituent | Paracetamol alone (P) | Paracetamol + citrate (PC) | Paracetamol + citrate + cysteine (PCC) |
|---|---|---|---|
| Paracetamol | 1 g | 1 g | 1 g |
| Sodium citrate | 0 | 0.070 g | qsp pH 5.5 (i.e. 0.07 g of citrate) |
| Chlorhydrate cysteine | 0 | 0 | 0.025 g |
| NaCl | 0.09 | 0.09 | 0.09 g |
| HCl or NaOH | qsp, pH 5.5 | qsp pH 5.5 | 0 |
| Inert gas | qsp $O_2$ approx. 0.5 ppm | qsp $O_2$ approx. 0.5 ppm | qsp $O_2$ approx. 0.5 ppm |
| Water | qsp 100 ml | qsp 100 ml | qsp 100 ml |

Packaging: under nitrogen (A) or under residual pressure of approx. 10,000 Pa

Sterlization at 121° C. for 15 minutes.

Results (after Sterilization):

a) the solutions P:PV (under vacuum) and PA (under nitrogen) are pink;

b) the solutions PC:PCV (citrate) are colourless and PCA (under nitrogen) is pink;

c) the solutions PCC:PCCV and PCCA are colourless but the residual cysteine content is higher when PCV is used.

Conclusion

For residual oxygen contents of the order of 0.5 ppm, the vacuum is in itself insufficient to ensure the stability of the paracetamol.

On the other hand, it acts synergically with citrate both with regard to the keeping properties of paracetamol and of cysteine.

## EXAMPLE VII

### Stability of Paracetamol Solution, and of Paracetamol Solution to which Sodium Citrate has been Added in the Presence of Nitrogen, or of Nitrogen Under a Vacuum

Preparation of the solutions:

| Constituent | Paracetamol (P) | Paracetamol – Citrate (PC) |
|---|---|---|
| Paracetamol (mg) | 1,000 | 1,000 |
| Trisodium citrate, $2H_2O$ (mg) | — | 70 |
| NaCl (mg) | 700 | 700 |
| HCl q.s.p. pH | 5.50 | 5.50 |
| $H_2O$ q.s.p. (ml) | 100 | 100 |

The solutions are produced under nitrogen (<0,50 ppm). Filling takes place under nitrogen, of volumes of 80 ml, into 100 ml bottles. Nitrogen is bubbled into the bottle for 30 seconds before stoppering.

Half the bottles are placed under an extreme vacuum before stoppering.

The solutions are heat sterilized at +120° C. for 15 minutes.

The solutions are stabilized at +25° C. and at +40° C.

Analysis at T=0

| Solution | Oxygen (ppm) | Residual pressure in Pa | pH |
|---|---|---|---|
| Paracetamol/nitrogen, not sterilized | 0.40 | — | 5.92 |
| Paracetamol/nitrogen, sterilized | 0.34 | — | 6.03 |
| Paracetamol/vacuum, not sterilized | 0.55 | <10,000 | 5.98 |
| Paracetamol/vacuum, sterilized | 0.50 | <10,000 | 6.28 |
| Paracetamol/Citrate/Nitrogen, not sterilized | 0.50 | — — | 5.50 |
| Paracetamol/Citrate/Nitrogen, sterilized | 0.60 | | 5.53 |
| Paracetamol/Citrate/vacuum, not sterilized | 0.36 | <10,000 | 5.50 |
| Paracetamol/Citrate/vacuum, sterilized | 0.40 | <10,000 | 5.54 |

HPLC analysis does not show the presence de peaks corresponding to degradation products (<0.01%).

Appearance of the Solutions after Keeping in Darkness at 25° C. for 2 Months

| Solution | coloration on D9 | coloration on D13 | coloration on D21 | coloration on D26 | coloration at 1 month | coloration at 2 months |
|---|---|---|---|---|---|---|
| Paracetamol/ Nitrogen sterilized | colourless | colourless | yellow hue | yellow hue | yellow + | yellow + |
| Paracetamol, placed under vacuum sterilized | colourless | colourless | colourless | colourless | colourless | yellow hue |
| Paracetamol/Citrate/ Nitrogen, sterilized | colourless | colourless | colourless | yellow hue Paracetamol/ Nitrogen | yellow hue | yellow + |
| Paracetamol/Citrate/ placed under vacuum, sterilized | colourless | colourless | colourless | colourless | colourless | colourless |

Conclusion

Only the citrate+vacuum combination ensures complete preservation of the paracetamol.

## EXAMPLE VIII

### Stability of the Paracetamol Solutions Protected by Sodium Citrate and Cysteine for Oxygen Concentrations of Approx. 1 ppm

Composition of the Solution

| Constituent | Quantity |
|---|---|
| Paracetamol (g) | 1 |
| Cysteine HCL, H20 (mg) | 25 |
| Sodium citrate, H20 (mg) | 70 |
| Sodium chloride (mg) | 700 |
| Water enough for | 100 ml |

Preparation of the solution takes place with continuous bubbling with nitrogen. It is filled into 100 ml bottles, under nitrogen, until a solution containing between 0.7 and 1.0 ppm of oxygen is obtained.

The bottles are then stoppered under a nitrogen atmosphere or under vacuum (approx. 10,000 Pa). Following sterilization at 121° C. for 15 minutes, the bottles are kept in darkness at 40° C. The colouration, the pH, the oxygen content and the residual cysteine content are evaluated immediately after sterilization, then after being stored for 14 days.

Results

| Solution | Coloration | pH | Oxygen (ppm) | Residual cysteine (%) |
|---|---|---|---|---|
| Solution under nitrogen, after sterilization | colourless | 5.53 | 0.85 | 75 |
| Solution under vacuum, after sterilization | colourless | 5.51 | 0.90 | 85 |
| Solution under nitrogen, after 14 days at 40° C. | yellow | 5.58 | 0.60 | 27 |
| Solution under vacuum, after 14 days at 40° C. | colourless | 5.59 | 0.90 | 85 |

Conclusion

Keeping under vacuum has a protective effect on the Paracetamol and the cysteine when the solution is kept under conditions of accelerated degradation. Conversely, preservation is insufficient under nitrogen. The vacuum seems to inhibit the oxidation reaction of the paracetamol and the cysteine, which confirms the reduction in residual oxygen under nitrogen, as compared with the maintenance of residual oxygen under vacuum.

## EXAMPLE IX

### 1% Dobutamine Sulphate Solution

A Dobutamine sulphate solution is prepared by dissolving 1 g Dobutamine in 50 ml of water and 19 ml of a 0.10% sodium ascorbate solution is added, with continuous bubbling of nitrogen. Then 25 mg hydrated cysteine chlorhydrate and 70 mg hydrated sodium citrate are added, then 700 mg sodium chloride to ensure isotonicity. The solution is made up to 100 ml by the addition of distilled water for injectable preparations.

It is filled into 100 ml bottles under nitrogen until the residual oxygen content is below 0.8 ppm. The bottles are then stoppered under vacuum (approx. 10,000 Pa) and sterilized at 121° C. for 20 minutes.

After removal from the autoclave, the bottles are kept in darkness in a thermostatic cupboard at 50° C.

An evaluation is made of absorption at 308 nm as an indication of oxidation into secondary products, the residual oxygen content and the residual cysteine content immediately after sterilization, then after being kept for 14 days at 50° C.

Results

There is no degradation of the Dobutamine in heat.

Using liquid chromatography the appearance of secondary peaks is established, detected by measuring the absorption at 308 nm, the degree of which decreases as the pH increases. Coloration remains slight and reduces as the pH increases.

What is claimed is:

**1**. A method for preparing an aqueous solution with an active nature susceptible to oxidation, which is paracetamol, while preserving for a prolonged period, comprising deoxygenation of the solution by bubbling with at least one inert gas and/or placing under vacuum, until the oxygen content is below 2 ppm, and optionally the aforementioned aqueous solution with an active principle is topped with an inert gas atmosphere heavier than air and placed in a closed container in which the prevailing pressure is 65,000 Pa maximum, and the oxygen content of the aqueous solution is below 2 ppm, and optionally the deoxygenation of the solution is completed by addition of an antioxidant.

**2**. The method for preparing a formulation of claim **1** wherein deoxygenation of the solution is completed by addition of a hydroxypolycarboxylic acid.

3. The method for preparing a formulation of claim 1 wherein the residual oxygen content of the aqueous solution is below 1 ppm.

4. The method for preparing a formulation of claim 1 wherein the residual oxygen content in the aqueous solution is equal to 0.5 ppm or below.

5. The method for preparing a formulation of claim 2 wherein the hydroxypolycarboxylic acid is selected from the group consisting of citric acid, tartaric acid, gluconic acid, saccharic acid, citramalic acid and malic acid.

6. The method for preparing a formulation of claim 2 wherein the hydroxypolycarboxylic acid is an acid or a salt thereof.

7. The method for preparing a formulation of claim 2 wherein the concentration of hydroxypolycarboxylic acid and/or one of its salts is 5 to 200 mg/100 ml of aqueous solution.

8. The method for preparing a formulation of claim 1 wherein the antioxidant is selected from the group consisting of thiols, derivatives of ascorbic acid and reducing sugars.

9. The method for preparing a formulation of claim 1 wherein the antioxidant is ascorbic acid or isoascorbic acid.

10. The method for preparing a formulation of claim 1 wherein the antioxidant is a mixture of cysteine and sodium citrate.

11. The method for preparing a formulation according to claim 1 comprising subjecting

an aqueous solution containing at least one phenolic active principle which is paracetamol, to which an antioxidant and a hydroxypolycarboxylic acid optionally have been added to extreme deoxygenation; introducing

under an inert gas atmosphere, part or all of the deoxygenated aqueous solution into a container previously cleared of the air contained therein; then stoppering

the container under an inert gas atmosphere, to create, in the closed container, a maximum pressure of 65,000 Pa to obtain

an aqueous solution with a phenolic acid principle in a placed closed container, in which the oxygen content is below or equal to 2 ppm.

12. The method of claim 10 wherein the deoxygenation is achieved by bubbling with an inert gas.

13. The method of claim 10, wherein the deoxygenation is achieved by application of vacuum.

14. The method of claim 10 wherein after stoppering, the solution is subjected to sterilization.

15. The method of claim 10 wherein the aqueous solution with an oxidizable active principle is subjected to sterilizing filtration under inert gas.

16. The method of claim 10 wherein the inert gas used for bubbling is nitrogen.

17. The method of claim 10 wherein the inert topping gas is heavier than air.

18. The method of claim 10 wherein the container is cleared of the air contained therein, by insufflation with an inert gas.

19. An injectable aqueous solutions containing, as an active ingredient, a principle of phenolic nature susceptible to oxidation, preserved by the method of claim 1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO. : 6,992,218 B2
APPLICATION NO. : 10/332060
DATED : January 31, 2006
INVENTOR(S) : Francois Dietlin and Daniele Fredj

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 12, line 54 in claim 1, "active nature" should read -- active principle of phenolic nature --.

Signed and Sealed this

First Day of September, 2009

David J. Kappos

David J. Kappos
*Director of the United States Patent and Trademark Office*

US006992218C1

# (12) EX PARTE REEXAMINATION CERTIFICATE (10694th)

# United States Patent

Dietlin et al.

(10) Number: US 6,992,218 C1

(45) Certificate Issued: Aug. 27, 2015

(54) **METHOD FOR OBTAINING AQUEOUS FORMULATIONS OF OXIDATION-SENSITIVE ACTIVE PRINCIPLES**

(75) Inventors: **Francois Dietlin**, La Vesinet (FR); **Daniele Fredj**, Gif sur Yvette (FR)

(73) Assignee: **PHARMATOP SCR**, Le Chesnay (FR)

**Reexamination Request:**
No. 90/013,107, Jan. 8, 2014

**Reexamination Certificate for:**

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|---|---|
| Patent No.: | **6,992,218** |
| Issued: | **Jan. 31, 2006** |
| Appl. No.: | **10/332,060** |
| PCT Filed: | **Jun. 6, 2001** |
| PCT No.: | **PCT/FR01/01749** |
| § 371 (c)(1), (2), (4) Date: | **Aug. 4, 2003** |
| PCT Pub. No.: | **WO01/93830** |
| PCT Pub. Date: | **Dec. 13, 2001** |

Certificate of Correction issued Sep. 1, 2009

(30) **Foreign Application Priority Data**

Jun. 6, 2000 (FR) ..... 00 07231

(51) **Int. Cl.**

| | |
|---|---|
| ***C07C 209/90*** | (2006.01) |
| ***A61K 9/00*** | (2006.01) |
| ***B01D 19/00*** | (2006.01) |
| ***A61K 47/22*** | (2006.01) |
| ***A61K 47/12*** | (2006.01) |
| ***A61K 31/05*** | (2006.01) |
| ***A61K 31/136*** | (2006.01) |
| ***A61K 31/167*** | (2006.01) |
| ***A61K 31/375*** | (2006.01) |
| ***A61K 33/00*** | (2006.01) |
| ***A61K 45/06*** | (2006.01) |

(52) **U.S. Cl.**
CPC ..... ***A61K 9/0019*** (2013.01); ***A61K 9/008*** (2013.01); ***A61K 31/05*** (2013.01); ***A61K 31/136*** (2013.01); ***A61K 31/167*** (2013.01); ***A61K 31/375*** (2013.01); ***A61K 33/00*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/12*** (2013.01); ***A61K 47/22*** (2013.01); ***B01D 19/0005*** (2013.01); *A61K 2300/00* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Number 90/013,107, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

*Primary Examiner* — Dwayne C. Jones

(57) **ABSTRACT**

A method for obtaining aqueous formulations with easily oxidizable active principles, notably phenols, stable over a prolonged period, comprising subjecting them to extreme deoxygenation by bubbling with an inert gas and/or placing wider vaccum, protecting them against possible resorption of oxygen by keeping them under an inert gas atmosphere, by filling, under inert gas, into bottles previously cleared of air by insufflation with inert gas, then subjecting them, while stoppering, to low pressure as obtained in the bottle, of 65,000 Pa maximum, to obtain aqueous solutions having a residual oxygen concentration in the solution below 2 ppm, and preferably of the order of 1 ppm and even 0.5 ppm useful as injectable preparations having an oxygen concentration in the solution below 2 ppm.

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**Attention is directed to the decision of The Federal Circuit's Decision dated March 23, 2015 in *Cadence Pharma. Inc. et al.* v. *Exela Pharmsci Inc. et al.*, Case No 2014-1184. This reexamination may not have resolved all questions raised by this decision. See 37 CFR 1.552(c) for *ex parte* reexamination and 37 CFR 1.906(c) for *inter partes* reexamination.**

# EX PARTE REEXAMINATION CERTIFICATE

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

**Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.**

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1-10** and **12-19** is confirmed.

Claim **11** is determined to be patentable as amended.

New claims **20-25** are added and determined to be patentable.

**11**. The method for preparing a formulation according to claim **1** comprising subjecting an aqueous solution containing at least one phenolic active principle which is paracetamol, to which an antioxidant and a hydroxypolycarboxylic acid optionally have been added to extreme deoxygenation; introducing under an inert gas atmosphere, part or all of the deoxygenated aqueous solution into a container previously cleared of the air contained therein; then stoppering the container under an inert gas atmosphere, to create, in the closed container, a maximum pressure of 65,000 Pa to obtain an aqueous solution with a phenolic acid principle in a placed closed container, in which the oxygen content is below [or equal to] 2 ppm.



*20. The method of claim 1 wherein the residual oxygen content is 0.5 to 1 ppm.*

*21. The method of claim 1 wherein the residual oxygen content is equal to or below 0.5 ppm.*

*22. The method of claim 1 wherein the residual oxygen content is equal to or below 0.05 ppm.*

*23. The method of claim 1 wherein the residual oxygen content is selected from the group consisting of 0.16 ppm, 0.2 ppm, 0.3 ppm, 0.4 ppm, 0.5 ppm, 0.6 ppm, 0.7 ppm, 0.8 ppm, 0.9 ppm and 1 ppm.*

*24. The method of claim 1 wherein the formulation is colorless.*

*25. The method of claim 2 wherein the hydroxypolycarboxylic acid is selected from the group consisting of citric acid, tartaric acid, gluconic acid, saccharic acid, citramalic acid and malic acid.*

* * * * *

# EXHIBIT B

US009399012B2

(12) **United States Patent**
**Royal et al.**

(10) **Patent No.: US 9,399,012 B2**
(45) **Date of Patent: Jul. 26, 2016**

(54) **REDUCED DOSE INTRAVENOUS ACETAMINOPHEN**

(75) Inventors: **Mike Allan Royal**, San Diego, CA (US); **James Bradley Breitmeyer**, Rancho Santa Fe, CA (US)

(73) Assignee: **MALLINCKRODT IP**, Dublin (IE)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1032 days.

(21) Appl. No.: **12/270,796**

(22) Filed: **Nov. 13, 2008**

(65) **Prior Publication Data**

US 2009/0143474 A1 Jun. 4, 2009

**Related U.S. Application Data**

(60) Provisional application No. 60/987,761, filed on Nov. 13, 2007.

(51) **Int. Cl.**

| | |
|---|---|
| ***A61K 31/16*** | (2006.01) |
| ***A61K 9/00*** | (2006.01) |
| ***A61K 47/02*** | (2006.01) |
| ***A61K 47/18*** | (2006.01) |

(52) **U.S. Cl.**

CPC ..... ***A61K 9/0019*** (2013.01); ***A61K 47/02*** (2013.01); ***A61K 47/18*** (2013.01); ***A61K 47/183*** (2013.01)

(58) **Field of Classification Search**

USPC ..... 514/629

See application file for complete search history.

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*Primary Examiner* — San-Ming Hui

(74) *Attorney, Agent, or Firm* — Mayer Brown LLP

(57) **ABSTRACT**

Described herein are compositions and methods for intravenous administration of acetaminophen at a single dose level of less than about 1000 mg for the treatment or prevention of pain (e.g., postoperative pain) and/or fever.

**109 Claims, No Drawings**

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# REDUCED DOSE INTRAVENOUS ACETAMINOPHEN

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is related to and claims priority to U.S. Provisional Patent Application No. 60/987,761, entitled "Reduced Dose Intravenous Acetaminophen" filed on Nov. 13, 2007, which is incorporated herein by reference in its entirety.

## BACKGROUND OF THE INVENTION

In the hospital, particularly in the postoperative setting, pain is a primary concern of patients. Opioid analgesics have been used to treat postoperative pain since 1784 and parenteral morphine has been a primary treatment modality since the 1850s. While opioids are highly effective in the treatment of many painful conditions, they have side effects and dose-dependent risks including nausea, vomiting, constipation, urinary retention, sedation, and respiratory depression. Similarly, non steroidal anti-inflammatory drugs (NSAIDs), including the older non selective (dual inhibitor) products and newer cyclo-oxygenase (COX)-2 products, have a variety of unwanted side effects especially when used in the perioperative setting. Non selective NSAIDs are associated with platelet dysfunction and the potential for bleeding at the surgical site, upper gastrointestinal ulcers and bleeding, edema, hypertension, congestive heart failure, renal dysfunction, severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, anaphylaxis, and most recently, an increased risk of thrombotic cardiovascular events.

## SUMMARY OF THE INVENTION

Described herein are pharmaceutical compositions having a reduced dose of acetaminophen for intravenous administration, and methods of using these compositions for treating and/or preventing pain and/or fever in a subject.

In some embodiments, the pharmaceutical compositions described herein comprise less than about 1 gram of acetaminophen, wherein the pharmaceutical composition is provided as a formulation suitable for intravenous administration. For example, various embodiments may comprise about 500 mgs to about 1 gram, or about 500 mgs to about 800 mgs, or about 500 mgs to about 750 mgs. In various embodiments, the pharmaceutical compositions described herein comprise about 600 mg to about 700 mg of acetaminophen.

In some embodiments, the pharmaceutical compositions described herein further comprise at least one antioxidant. In some embodiments, the at least one antioxidant comprises cysteine hydrochloride monohydrate, thiolyglycolic acid, thiolacetic acid, dithiothreitol, reduced glutathione, thiourea, alpha-thioglycerol, cysteine, acetylcysteine, or mercaptoethane sulfonic acid, ascorbic acid ascorbic acid derivatives, an organic compound having at least one thiol, an alkyl polyhydroxylated compound, or a cycloalkyl polyhydroxylated compound.

In some embodiments, the pharmaceutical composition further comprises a buffering agent (e.g., disodium phosphate dehydrate). In some embodiments, the pharmaceutical composition has a pH from about 4 to about 8 when in solution. In some embodiments, the pharmaceutical composition has a pH of about 5 to about 6 when in solution.



In some embodiments, the pharmaceutical composition has an osmolality from about 250 mOsm/L to about 400 mOsm/L when in solution. In some embodiments, the pharmaceutical composition further comprises an isotonicity agent. In some embodiments, the isotonicity agent is dextrose, mannitol, or lactose.

In some embodiments, the pharmaceutical composition further comprises at least one analgesic agent other than acetaminophen. In some embodiments, the at least one analgesic agent other than acetaminophen comprises an anilide, an opioid, an NSAID, a cannabinoid, a pyrazolone, or a barbiturate.

In some embodiments, the pharmaceutical composition further comprises EDTA.

In a further aspect provided herein is a method for preventing or reducing pain or fever in a subject in need thereof, comprising administering to the subject, by an intravenous route of administration, a pharmaceutical compositions described herein. In some embodiments, the administration is repeated at least once with an interval of about 3 to about 5 hours. In some embodiments, the administration is repeated at least six times in a period of twenty four hours. In various embodiments, the administration is repeated three to eight times (e.g., 3 times, 4 times, five times, six times, seven times, or eight times) in a period of twenty four hours and about 3 to about 5 grams of acetaminophen (e.g., about 3 grams, about 4 grams or about 5 grams) is delivered over the twenty four hour period. In other embodiments, the administration is repeated three to eight times in a period of twenty four hours and less than about 4 grams of acetaminophen is delivered over the twenty four hour period.

In some embodiments, the pharmaceutical formulation for IV administration is a solution comprising: about 600 mg to about 700 mg of acetaminophen, cysteine hydrochloride monohydrate, disodium phosphate dehydrate, and mannitol, wherein the solution has a pH of between about 5 and about 6 and an osmolality of between about 200-400 mOsm/L. In some embodiments, the pharmaceutical composition in solution has an acetaminophen concentration of about 0.5% (w/v) to about 10% (w/v). In some embodiments, the acetaminophen concentration is about 1% (w/v). In some embodiments, the pharmaceutical composition to be administered further comprises EDTA.

In some embodiments, the subject to be treated is suffering from an infection. In some embodiments, the subject to be treated is suffering from a fever. In some embodiments, the subject to be treated is unconscious, sedated, fasting, nauseous, or unable to be administered a pharmaceutical composition by an oral route.

In some embodiments, the pharmaceutical composition is administered to the subject after a surgical intervention. In some embodiments, the pharmaceutical composition is administered within three hours of a surgical intervention on the subject. In some embodiments, the pharmaceutical composition is administered within 1 hour of a surgical intervention on the subject. In some embodiments, the pharmaceutical composition is administered postoperatively. In some embodiments, the subject to be treated is suffering from postoperative pain.

In various embodiments the pharmaceutical compositions described herein are administered as a pretreatment.

In another aspect provided herein is a method for preventing or reducing pain or fever in a subject in need thereof, comprising administering to the subject, by an intravenous route of administration, a pharmaceutical composition described herein.

## INCORPORATION BY REFERENCE

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

## DETAILED DESCRIPTION OF THE INVENTION

To date, the standard intravenous (IV) dose of acetaminophen for the relief of pain or fever has been 1000 mg in adults and adolescents weighing at least 50 kg. At this dose level, the frequency of acetaminophen administration is limited to a maximum of once every six hours (i.e., four administrations per twenty four hours) to minimize the potential for hepatotoxicity. On the other hand, it has generally been noted that acetaminophen has greatest efficacy during its initial rise in plasma concentration, i.e., during the first few hours post-administration, and is less effective later on after the plasma concentration of the drug drops from its peak. While not wishing to be bound by theory, it is thought that this change in efficacy is likely due to a time and concentration-dependent modulation of the central and peripheral nociceptive pathways through which acetaminophen acts.

Further, if the duration of effect of a 1000 mg dose of acetaminophen is shorter in duration than 6 hours, the use of this dose is limited since dosing more frequently than every 6 hours, e.g., every 4 hours, leaves a gap in coverage due to the 4 g acetaminophen maximum daily limit. In the treatment of fever, a dose less than 1000 mg may be fully effective due to the fact that a lower plasma level (compared to that needed for pain) is needed to effectively reduce fever.

Thus, intravenous administration of a reduced dose of acetaminophen, as described herein, permits more frequent IV acetaminophen administration to yield better overall relief of symptoms for many patients while avoiding any potential gap artificially created by the daily limit.

Also, the reduced acetaminophen IV dose affords greater flexibility to the physician in customizing treatments to the needs of the patient, selecting the dose of other drugs for use in combination therapies and allowing for smoother transitions to oral products containing acetaminophen.

Accordingly, described herein are reduced IV dose formulations of acetaminophen for intravenous administration and the use of reduced IV doses of acetaminophen for use for the treatment or prevention of pain and/or fever.

Certain Terminology

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. In the event that there is a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet or other appropriate reference source. Reference thereto evidences the availability and public dissemination of such information.

It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. It should also be noted that use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes", and "included" is not limiting.



Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY $4^{TH}$ ED." Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, IR and UV/Vis spectroscopy and pharmacology, within the skill of the art are employed. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

The terms "treat," "treating" or "treatment," and other grammatical equivalents as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition, and are intended to include prophylaxis. The terms further include achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more.

The terms "effective amount," "therapeutically effective amount" or "pharmaceutically effective amount" as used herein, refer to a sufficient amount of at least one agent or compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising the compound as disclosed herein required to provide a clinically significant decrease in pain. An additional example is that an "effective amount" may be a dosage that decreases a fever. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

The terms "administer," "administering," "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods

include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein, e.g., as discussed in Goodman and Gilman, The Pharmacological Basis of Therapeutics, current ed.; Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa. In preferred embodiments, the compositions comprising acetaminophen as described herein are administered intravenously.

The term "acceptable" as used herein, with respect to a formulation, composition or ingredient, means having no persistent detrimental effect on the general health of the subject being treated.

The term "antioxidant" refers to a compound that prevents oxygen or oxygen-derived free radicals from interacting with other substances. Antioxidants are added to minimize or retard oxidative processes that occur with some drugs or excipients upon exposure to oxygen or in the presence of free radicals. These processes can often be catalyzed by light, temperature, hydrogen on concentration, presence of trace metals or peroxides.

The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

"Concurrent administration," "administered in combination" or similar phrases referring to the acetaminophen and at least one additional component means that the components are administered concurrently to the mammal being treated. By "concurrently," it is meant that each component may be administered at the same time or sequentially in any order at different points in time. However, if not administered at the same time, they should be administered sufficiently closely in time so as to provide the desired enhancement of treatment effect. Suitable dosing intervals and the order of administration with such compounds will be readily apparent to those skilled in the art, once armed with the present disclosure. Preferably both components are administered at the same time or within the same hour.

As used herein, the term "animal" shall refer to a vertebrate animal. More preferably, the vertebrate animal is a mammal. As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human.

As used herein, the term "pain" shall refer to all types of pain, including, but not limited, to nociceptive pain, neuropathic pain, post-operative pain, lower back pain, cluster headaches, herpes neuralgia, phantom limb pain, central pain, dental pain, opioid-resistant pain, visceral pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns, including sunburn, post partum pain, migraine, and genitourinary tract-related pain including cystitis. Levels of pain in a subject can be quantified using standard subjective assay scales of pain including, e.g., the Pain Intensity Visual Analogue Scale or Pain Intensity Categorical Scale. Likewise, levels of "pain relief" can also be quantified by a subjective assay, e.g., Time to Perceptible and Meaningful Pain Relief.

The terms "intravenous formulation," or "intravenous acetaminophen formulation" shall refer to a single dose formulation of acetaminophen that is provided as a lyophilized powder (or other solid form) that, once reconstituted in solution, is physiologically compatible with intravenous administration (e.g., by injection, infusion or otherwise). Alternatively, the terms refer to a formulation that is provided as a solution.

Reduced Dose Acetaminophen Formulations for Intravenous Administration (IV Formulations)

In some embodiments, the IV acetaminophen formulations described herein are in the form of a lyophilized powder to be reconstituted in solution under sterile conditions prior to administration. In other embodiments, the IV acetaminophen formulations are provided as sterile solutions ready for administration. Appropriate containers (e.g., vials, bottles, ampules, containers, etc.) for the IV formulations in either of the forms just described, as well as aseptic techniques are well known.

IV Acetaminophen Dosage

In various embodiments, the single dose IV acetaminophen formulation contains less than about 1 gram of acetaminophen. In some embodiments, the single dose IV acetaminophen contains about 500 to about 1000 mgs. In some embodiments, the single dose IV acetaminophen contains about 550 mgs to about 900 mgs. In some embodiments, the single dose IV acetaminophen formulations described herein contain about 550 mg to about 800 mg of acetaminophen, i.e., about 560 mg, 570 mg, 580 mg, 600 mg, 610 mg, 620 mg, 630 mg, 640 mg, 650 mg, 660 mg, 670 mg, 675 mg, 680 mg, 690 mg, 700 mg, 720 mg, 750 mg, 775 mg, or any other amount of acetaminophen from about 550 mg to about 800 mg of acetaminophen. In some embodiments, an IV acetaminophen formulation contains about 600 mg to about 700 mg of acetaminophen, i.e., about 610 mg, 620 mg, 630 mg, 640 mg, 650 mg, 660 mg, 670 mg, 680 mg, 690 mg, or any other amount of acetaminophen from about 600 mg to about 700 mg of acetaminophen. In one embodiment, the acetaminophen formulation contains about 650 mg of acetaminophen.

In some embodiments, the concentration of acetaminophen in an IV formulation solution described herein is about 0.3% (w/v) to about 12% (w/v), i.e., about 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.5%, 2.5%, 3%, 3.7%, 4%, 4.5%, 5%, 6%, 7%, 8%, 8.5%, 9%, 10%, 10.5%, 11%, or any other concentration from about 0.3% (w/v) to about 12% (w/v). In some embodiments the concentration of acetaminophen is about 0.7% (w/v) to about 1.4% (w/v), i.e., about 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3% or any other concentration of acetaminophen from about 0.7% (w/v) to about 1.4% (w/v). In one embodiment, the concentration of acetaminophen is about 1.0% (w/v).

In some embodiments, the volume of an IV acetaminophen formulation solution is about 30 to about 200 ml, i.e., about 30, 35, 40, 45, 55, 60, 65, 75, 80, 85, 90, 92, 95, 100, 105, 110, 125, 130, 150, 175, 180, or another volume of IV formulation solution from about 30 to about 200 ml. In some embodiments, the volume of the IV formulation is about 75 to about 125 ml. In another embodiment the volume is about 40 to about 75 ml. In one embodiment, the volume of the IV formulation is about 100 ml.

Antioxidants

Generally, the acetaminophen formulations described herein also contains at least one antioxidant to increase the stability of acetaminophen in solution. Examples of suitable antioxidants include, but are not limited to, cysteine hydrochloride monohydrate, thiolyglycolic acid, thiolacetic acid,

dithiothreitol, reduced glutathione, thiourea, alpha-thioglycerol, cysteine, acetylcysteine, methionine, mercaptoethane sulfonic acid, metabisulfite, ascorbic acid ascorbic acid derivatives (e.g., ascorbyl palmitate), sodium citrate, an organic compound having at least one thiol, an alkyl polyhydroxylated compound, a cycloalkyl polyhydroxylated compound, a hydroxypolycarboxylic acid, an alpha-hydroxypolycarboxylic acid (e.g., citric acid), tocotrienol, dimethyl glycine, betaine, butylated hydroxyanisole, butylated hydroxytoluene, tocopherol, tocopherol polyethylene glycol succinate, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, dithiocarbamates or any combination thereof. In one embodiment, the acetaminophen formulation is free of polyethylene glycol or a derivative thereof. In another embodiment, the acetaminophen formulation is free of sulfites. In one embodiment, the antioxidant is cysteine hydrochloride monohydrate. In yet another embodiment, the antioxidant is mannitol.

In some embodiments, the amount % (w/w) of the antioxidant in the solid form of the IV formulation (i.e., prior to preparation in solution) is about 0.10% (w/w) to about 5.0% (w/w), i.e., 0.15% (w/w), 0.17% (w/w), 0.20% (w/w), 0.30% (w/w), 0.40% (w/w), 0.45% (w/w), 0.50% (w/w), 0.52% (w/w), 0.55% (w/w), 0.60% (w/w), 0.70% (w/w), 0.80% (w/w), 1.0% (w/w), 1.3% (w/w), 1.5% (w/w), 1.7% (w/w), 2.0% (w/w), 2.2% (w/w), 2.3% (w/w), 2.5% (w/w), 2.7%, 2.8%, 3.0% (w/w), 3.2%, 3.5% (w/w), 3.6% (w/w), 4.0% (w/w), 4.7% (w/w), or any other amount of antioxidant % (w/w) from about 0.10% (w/w) to about 5.0% (w/w). In some embodiments, the amount % (w/w) of antioxidant is about 0.30% (w/w) to about 1.0% (w/w). In one embodiment, the amount % (w/w) of antioxidant is about 0.50% (w/w).

In some embodiments, the concentration of the antioxidant in an IV formulation solution prior to administration ranges from about 0.01 mg/ml to about 10 mg/ml, i.e., 0.02 mg/ml, 0.03 mg/ml, 0.05 mg/ml, 0.08 mg/ml, 0.09 mg/ml, 0.10 mg/ml, 0.12 mg/ml, 0.13 mg/ml, 0.15 mg/ml, 0.18 mg/ml, 0.20 mg/ml, 0.22 mg/ml, 0.25 mg/ml, 0.27 mg/ml, 0.30 mg/ml, 0.40 mg/ml, 0.45 mg/ml, 0.50 mg/ml, 0.60 mg/ml, 0.80 mg/ml, 1.2 mg/ml, 1.5 mg/ml, 2.0 mg/ml, 2.5 mg/ml, 3.0 mg/ml, 3.5 mg/ml, 4.0 mg/ml, 5.0 mg/ml, 6.0, mg/ml 7.5 mg/ml, 8.0 mg/ml, 9 mg/ml, 9.5 mg/ml, or any other concentration of antioxidant from about 0.01 mg/ml to about 10 mg/ml. In some embodiments, the concentration of antioxidant is about 0.08 mg/ml to about 0.50 mg/ml. In one embodiment, the concentration of antioxidant is about 0.25 mg/ml.

Buffering Agents

In some embodiments, an IV acetaminophen formulation contains at least one buffering agent to maintain the pH of the formulation within an acceptable range as described herein. The buffer used is a buffer compatible with parenteral administration in humans, the pH of which may be adjusted between 4 and 8. In some embodiments, the pH of an IV acetaminophen formulation is from about pH 4 to about pH 8, i.e., pH 4.5, pH 4.6, pH 4.8, pH 5.0, pH 5.5, pH 6.2, pH 6.5, pH 7.5, or any other pH value from about pH 4 to about pH 8. In some embodiments, the pH of the IV acetaminophen formulation is from about pH 5 to about pH 7.0, i.e., about pH 5.2, pH 5.5, pH 5.6, pH 6.0, pH, 6.4, or any other pH value from about pH 5 to about pH 7.0. In one embodiment, the IV acetaminophen formulation has a pH of about 5 to about 6.

In some embodiments, buffering agents have a pKa from about 4.5 to about 6.5, i.e., 4.6, 4.8, 5.0, 5.2, 5.3, 5.4, 5.5, 5.8, 6.0, 6.2, 6.4, or any other pKa from about 4.5 to about 6.5.

In some embodiments, the buffering agent is a pharmaceutically acceptable salt or acid of citrate, phosphate, acetate, glutamate, tartrate, benzoate, lactate, histidine or other amino acids, gluconate, malate, succinate, formate, propionate, carbonate, or any combination thereof adjusted to an appropriate pH, as described herein, with acid (e.g., hydrochloric acid) or base (e.g., sodium hydroxide) as required. In one embodiment, the buffering agent is disodium phosphate dehydrate.

In some embodiments, the amount % (w/w) of the buffering agent in the solid form of the IV formulation (i.e., prior to preparation in solution) is about 0.05% (w/w) to about 2% (w/w), i.e., about 0.08% (w/w), 0.10% (w/w), 0.15% (w/w), 1.0% (w/w), 1.3% (w/w), 1.5% (w/w), 1.7% (w/w), 0.20% (w/w), 0.22% (w/w), 0.25% (w/w), 0.26% (w/w), 0.27% (w/w), 0.28% (w/w), 0.30% (w/w), 0.35% (w/w), 0.40% (w/w), 0.50% (w/w), 0.60% (w/w), 0.70% (w/w), 0.80% (w/w), 1.2% (w/w), 1.4% (w/w), 1.5% (w/w), 1.7%, or any other amount of buffering agent % (w/w) from about 0.05% (w/w) to about 2.0% (w/w). In some embodiments, the amount % (w/w) of the buffering agent is about 0.10% to about 0.70%. In one embodiment, the amount % (w/w) of the buffering agent is about 0.26%.

In some embodiments, the concentration of the buffering agent in an IV formulation solution prior to administration ranges from about 0.01 mg/ml to about 10 mg/ml, i.e., 0.02 mg/ml, 0.03 mg/ml, 0.05 mg/ml, 0.08 mg/ml, 0.09 mg/ml, 0.10 mg/ml, 0.12 mg/ml, 0.13 mg/ml, 0.15 mg/ml, 0.30 mg/ml, 0.5 mg/ml, 0.8 mg/ml, 1.2 mg/ml, 1.5 mg/ml, 2.0 mg/ml, 2.5 mg/ml, 3.0 mg/ml, 3.5 mg/ml, 4.0 mg/ml, 5.0 mg/ml, 6.0, mg/ml 7.5 mg/ml, 8.0 mg/ml, 9 mg/ml, 9.5 mg/ml, or any other concentration of buffering agent from about 0.01 mg/ml to about 10 mg/ml. In some embodiments, the concentration of buffering agent is about 0.08 mg/ml to about 0.30 mg/ml. In one embodiment, the concentration of buffering agent is about 0.13 mg/ml.

Isotonicity Agents

In some embodiments, an IV acetaminophen formulation also contains one or more isotonicity agents to maintain the osmolality of the formulation in a range that is physiologically compatible with IV administration. In some embodiments, the osmolality of the IV acetaminophen formulation is about 230 mOsm/L to about 420 mOsm/L, i.e., about 240 mOsm/L, 250 mOsm/L, 260 mOsm/L, 270 mOsm/L, 280 mOsm/L, 290 mOsm/L, 300 mOsm/L, 305 mOsm/L, 310 mOsm/L, 320 mOsm/L, 350 mOsm/L, 375 mOsm/L, 400 mOsm/L or any other osmolality from about 240 mOsm/L to about 420 mOsm/L. In some embodiments, the osmolality of the IV acetaminophen formulation is about 280 mOsm/L to about 320 mOsm/L, i.e., about 290 mOsm/L, 295 mOsm/L, 300 mOsm/L, 305 mOsm/L, 310 mOsm/L, 315 mOsm/L, or any other osmolality from about 280 mOsm/L to about 320 mOsm/L. In one embodiment, the osmolality of the IV acetaminophen formulation is about 200-400 mOsm/L.

Suitable agents for adjusting the isotonicity of IV acetaminophen formulations include, but are not limited to, mannitol, sorbitol, glycerol, sucrose, glucose, dextrose, levulose, fructose, lactose, polyethylene glycols 400 to 4000, phosphates, sodium chloride, potassium chloride, calcium chloride, calcium gluconoglucoheptonate, dimethyl sulfone. In one embodiment, the isotonicity agent is mannitol.

In some embodiments, the amount % (w/w) of the isotonicity agent in the solid form of the IV formulation (i.e., prior to preparation in solution) is about 5% (w/w) to about 95% (w/w), i.e., about 10% (w/w), 15% (w/w), 20% (w/w), 25% (w/w), 30% (w/w), 35% (w/w), 40% (w/w), 45% (w/w), 50% (w/w), 55% (w/w), 60% (w/w), 65% (w/w), 70% (w/w), 72% (w/w), 74% (w/w), 76% (w/w), 78% (w/w), 79% (w/w), 80%

(w/w), 81% (w/w), 82% (w/w), 84% (w/w), 86% (w/w), 90% (w/w), 92% (w/w), or any other amount of isotonicity agent % (w/w) from about 5% (w/w) to about 95% (w/w). In some embodiments, the amount of isotonicity agent % (w/w) is about 65% (w/w) to about 85% (w/w). In one embodiment, the amount of isotonicity agent % (w/w) is about 79%.

In some embodiments, the concentration of the isotonicity agent in an IV formulation solution prior to administration ranges from about 1.0 mg/ml to about 150 mg/ml, i.e., 1.0 mg/ml, 2.0 mg/ml, 3.0 mg/ml, 3.5 mg/ml, 4.0 mg/ml, 4.5 mg/ml, 5.0 mg/ml, 8.0 mg/ml, 12 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 32 mg/ml, 35 mg/ml, 37 mg/ml, 38 mg/ml, 40 mg/ml, 50 mg/ml, 60, mg/ml, 75 mg/ml, 80 mg/ml, 90 mg/ml, 95 mg/ml, 100, 110, 120, 140, or any other concentration of buffering agent from about 5 mg/ml to about 150 mg/ml. In some embodiments, the concentration of buffering agent is about 0.08 mg/ml to about 0.30 mg/ml. In one embodiment, the concentration of buffering agent is about 0.13 mg/ml.

Stabilizers

In some embodiments, IV acetaminophen formulations described herein also include a stabilizer, e.g., a chelating agent such as ethylene diamino tetraacetic acid (EDTA), ethylene diamino, N,N'-diacetic-N,N'-dipropionic acid, ethylene diamino tetraphosphonic acid, 2,2'-(ethylene diamino) dibutyric acid, nitrilotriacetic, acid, or ethylene-glycol bis (diaminoethyl ether) N,N,N',N'-tetraacetic acid and sodium or calcium salts thereof. In some embodiments, the IV acetaminophen formulation includes EDTA as the stabilizer.

In some embodiments, the IV acetaminophen formulations described herein contain a stabilizer in the amount of about 0.005 to about 1.0 mg/ml. In some embodiments, the stabilizer is present in an amount of about 0.01 mg/ml, 0.05 mg/ml, 0.1 mg·ml, 0.5 mg/ml, or 1.0 mg/ml.

In some embodiments, to reduce oxidation of acetaminophen in solution and thereby increase its stability, oxygen is removed from an IV formulation solution by bubbling an inert gas (e.g., argon or nitrogen) through the solution under sterile conditions. Methods for minimizing oxidative degradation of acetaminophen solutions during storage are described in further detail in, e.g., U.S. Pat. No. 6,992,218, which is incorporated herein by reference in its entirety.

Methods of Treatment

In many cases, IV administration of acetaminophen is considered the most suitable route of administration for expedient and efficacious relief of a patient's pain or fever, particularly in a hospital setting. In some embodiments, a subject to be administered an IV formulation of acetaminophen (e.g., an adult subject or adolescent weighing at least about 50 kg), as described herein, is unconscious, sedated, fasting, nauseous, or unable to be administered a pharmaceutical composition by an oral route. Additionally, the rectal route is associated with highly variable bioavailability and slow absorption, and in children, the efficacious rectal dose exposes some pediatric patients to a potentially toxic exposure. In some embodiments, a patient suffering from pain or fever is in need of a faster onset of pain relief or fever treatment than possible by acetaminophen administration through an administration route other than by an IV administration.

In some embodiments, the IV formulations described herein are used as a pretreatment to another therapy. In some of these embodiments, pretreatment with an IV formulation described herein allows the use of a lower dose of acetaminophen. In some embodiments, the IV formulation described herein is administered before chemotherapy treatment, radiation treatment, a biopsy, or a blood transfusion. It should be understood that these are non-limiting examples and that the IV formulations described herein can be administered as a pretreatment to any therapy where pain and/or fever are predicted to occur.

The IV formulations described herein can be used for reducing pain conditions including, but not limited to, acute nociceptive pain, acute neuropathic pain, postoperative pain, lower back pain, cluster headaches, herpes neuralgia, phantom limb pain, central pain, dental pain, opioid-resistant pain, visceral pain, surgical pain, procedural pain, bone injury pain, pain during labor and delivery, pain resulting from burns, post partum pain, headache, muscular aches, backache, arthritis pain, the common cold, toothache, dental pain, osteoarthritis pain, menstrual pain, menstrual cramps, migraine, and genitourinary tract-related pain including cystitis. In some embodiments, the IV formulation is administered preemptively to a subject, i.e., prior to the onset of pain or a pain-inducing condition or stimulus (e.g., a surgical operation). In some embodiments, the IV formulations described herein are used to reduce fever, including, but not limited to, fever due to infections, drug reactions, allergic reactions, transfusion reactions, stroke, surgery, heat stroke, rheumatic diseases, cancer, or fever of unknown origin. In some embodiments, the IV formulations described herein are administered to a patient undergoing a dental procedure.

In some embodiments, the IV formulation is administered to a subject after undergoing a surgical intervention, e.g., within about 12 hours after a surgical intervention, i.e., within 11 hours, 10 hours, 9 hours, 8 hours, 6 hours, 5 hours, 4 hours, 3 hours, 2 hours, 1 hours, 45 minutes, 30 minutes 15 minutes, 5 minutes, or any period within about 12 hours following a surgical intervention.

In some embodiments, a subject is administered the IV formulation prior to a surgical intervention, e.g., about 4 hours or less prior to the surgical intervention, i.e., about 3 hours, 2 hours, 1 hours, 30 minutes, 15 minutes or even during the surgical intervention itself.

Depending on the concentration of acetaminophen in an IV formulation solution and consistent with the acetaminophen dose levels described herein, the volume of IV formulation solution to be administered can vary from about 1 mL to about 200 mL, e.g., 5 mL, 10 mL, 20 mL, 25 mL, 30 mL, 40 mL, 50 mL, 60 mL, 65 mL, 70 mL, 85 mL, 90 mL, 100 mL, 110 mL, 120 mL, 130 mL, 140 mL, 150 mL, 160 mL, 180 mL, or any other volume of IV formulation solution from about 1 mL to about 200 mL.

In some embodiments, the amount of time required for administration of the IV formulation ranges from about 1 minute to about 1 hours, i.e., about 5 minutes, 10 minutes, 11 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, or any other administration time from about 1 minute to about 1 hour. In some embodiments, the amount of time required for administration of the IV formulation ranges from about 5 minutes to about 45 minutes, or about 5 minutes to about 30 minutes, or about 5 minutes to about 15 minutes.

Depending on the severity and persistence of a subject's condition, and in accordance with a medical caregiver's judgment, an IV formulation dose of acetaminophen, as described herein, can be administered in an interval to allow for the administration of about 3 to about 5 grams in a 24 hour period. In some embodiments, the IV formulation of acetaminophen is administered in an interval sufficient to allow for the administration of about 4 grams in a 24 hour period. In some embodiments, the IV formulation is administered between 1 to 6 times, i.e., 1, 2, 3, 4, 5, 6 times every twenty four hours, as deemed necessary by a medical caregiver. In some embodiments, the frequency of administration is not greater than once every four hours.

In various embodiments, the IV formulation of acetaminophen is dosed so as to provide less than about 4 grams over a 24 hour period. In various embodiments, the IV formulation of acetaminophen is dosed three to six times in a 24 hour period. For example, in some embodiments, the IV formulation of acetaminophen is dosed three times in a 24 hour period. In other embodiments, the IV formulation of acetaminophen is dosed four times in a 24 hour period. In still other embodiments, the IV formulation of acetaminophen is dosed five times in a 24 hour period. In some embodiments, the IV formulation of acetaminophen is dosed six times in a 24 hour period. In some embodiments, the IV formulation of acetaminophen is dosed seven times in a 24 hour period. In some embodiments, the IV formulation of acetaminophen is dosed eight times in a 24 hour period.

Combination Therapies

The acetaminophen IV formulations described herein can also be used in combination with other therapeutic reagents, e.g., other analgesics, antipyretics, or anti-inflammatory agents that are selected for their therapeutic or palliative value. In general, where a combination therapy is employed, other agents do not have to be administered in the same pharmaceutical composition as acetaminophen, and may, because of different physical and chemical characteristics, be administered by different routes. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician with the teachings described herein. The initial administration of either the IV acetaminophen formulation or the one or more therapeutic agents (e.g., analgesic agents other than acetaminophen) to be used in combination with acetaminophen can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The particular choice of compounds (e.g., analgesic agents) for use in combination with the IV acetaminophen formulation described herein will depend on the diagnosis of the attending physicians (or other medical caregivers) and their judgment of the condition of the patient and the appropriate treatment protocol. The compounds may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the severity of pain experienced by the patient, the nature of the disease, disorder, or condition, the condition, and the actual choice of compounds used. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient.

For combination therapies described herein, dosages of the compounds to be co-administered with an acetaminophen IV formulation will vary depending on the type of co-drug employed, on the amount of pain experienced by the patient, the risk for addiction, the disease or condition being treated and so forth. In addition, when co-administered with one or more biologically active agents, the acetaminophen IV formulation provided herein may be administered either simultaneously with the biologically active agent(s), or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein in combination with the biologically active agent(s).

In any case, the multiple therapeutic agents (one of which is an acetaminophen IV formulation described herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified IV form, or in multiple forms (by way of example only, either as a single IV formulation, as multiple IV formulations, or as IV formulation and a pill). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may vary from more than 1 minute to less than 12 hours. In some embodiments, the timing between the multiple doses is from between about 1 minute to about 6 hours, or about 1 minute and about 3 hours, or about 1 minute and about 1 hour. In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents; the use of multiple therapeutic combinations is also envisioned.

The pharmaceutical agents which make up the combination therapy disclosed herein may be a combined dosage form (i.e., a combined IV formulation) or in separate dosage forms intended for substantially simultaneous administration. The pharmaceutical agents that make up the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two-step administration. The two-step administration regimen may call for sequential administration of the active agents or spaced-apart administration of the separate active agents. The time period between the multiple administration steps may range from, a few minutes to several hours, depending upon the properties of each pharmaceutical agent, such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the pharmaceutical agent.

The compounds described herein and combination therapies can be administered before, during or after the occurrence of a fever or painful condition, and the timing of administering the composition containing a compound can vary. Thus, for example, the compounds can be used as a prophylactic and can be administered continuously to subjects with a propensity to develop conditions (e.g., body aches and chills following chemotherapy treatment) or diseases in order to prevent the occurrence of the disease or condition. The compounds and compositions can be administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the compounds can be initiated within the first 48 hours of the onset of the symptoms, preferably within the first 48 hours of the onset of the symptoms, more preferably within the first 6 hours of the onset of the symptoms, and most preferably within 3 hours of the onset of the symptoms.

A compound is preferably administered as soon as is practicable before or after the onset of a painful condition (e.g., postoperative pain), and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months.

Exemplary Analgesic Agents for Use in Combination with an Acetaminophen IV Formulation

Opioids

In some embodiments, an acetaminophen IV formulation described herein is used in any combination with one or more opioids, which include, but are not limited to allylprodine, alphamethylfentanyl, alfentanil, bezitramide, buprenorphine, butorphanol, carfentanyl, codeine, dextropropoxyphene, dextromoramide, dezocine, diacetylmorphine, dihydrocodeine, dipapanone, dismorphine, dihydrocodeine, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, lefetamine, levorphanol, levo-alphacetylmethadol, levomethorphan, meptazinol, methadone, morphine, nalbuphine, nicomorphine, ohmefentanyl, opium, oripavine, oxycodone, oxymorphone, methadone, PEPAP, pentazocine, pethidine,

phenazocine, piritamide, prodine, propoxyphene napsylate, remifentanil, sufentanil, tilidine, thebaine, tramadol, and tapentadol.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

In some embodiments, an acetaminophen IV formulation described herein is used in any combination with one or more NSAIDs, which include, but are not limited to amoxiprin, benorilate, choline magnesium salicylate, diflusinal, faislamine, methyl salicylate, magnesium salicylate, salicyl salicylate, diclofenac, aceclofenac, acemetacin, bromfenac, ethenzamide, etodolac, indometacin, nabumetone, sulindac, tolmetin, carprofen, fenbufen, fenoprofen, flurbiprofen, ketoprofen, ketorolac, loxoprofen, naproxen, oxaprozin, tiaprofenic acid, suprofen, mefenamic acid, meclofenamic acid, phenylbutazone, metamizole, oxyphenbutazone, sulfinpyrazone, piroxicam, lornoxicam, meloxicam, tenoxicam, nimesulide salixylates, arylalkanoic acids, 2-arylpropionic acids (profens), n-arylanthranilic acids (fenamic acids), pyrazolidine derivatives, oxicams, and COX-2 inhibitors.

Other Analgesic Agents

In some embodiments, an acetaminophen iv formulation described herein is used in any combination with one or more analgesic agents not described above, including, but not limited to, barbiturates (e.g., butalbital), pyrazolones (e.g., aminophenazone, metamizole, phenazone), cannabinoids (e.g., tetrahydrocannabinol), ziconotide, choline magnesium fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, morphine, desomorphine, apomorphine, diamorphine, pethidine, methadone, dextropropoxyphene, pentazocine, dextromoramide, oxymorphone, hydromorphone, dihydromorphine, noscapine, papverine, papveretum, alfentanil, buprenorphine, tramadol and pharmaceutically acceptable salts, derivatives, homologs or analogs thereof as well as opioid agonists.

Exemplary Antiemetic Agents for Use in Combination with an Acetaminophen IV Formulation

In some embodiments, an acetaminophen iv formulation described herein is used in any combination with one or more antiemetic agents not described above, including, but not limited to, antihistamines (e.g., Cyclizine, Diphenhydramine, Dimenhydrinate, Meclizine, Promethazine, Pentazine, Phenergan, Promacot, or Hydroxyzine); 5-$HT_3$ receptor antagonists (e.g., Dolasetron, Granisetron, Ondansetron, Tropisetron, or Palonosetron); and dopamine antagonists (e.g., Domperidone, Droperidol, haloperidol, chlorpromazine, promethazine, prochlorperazine, or metoclopramide).

Kits

In some embodiments provided herein are kits that can simplify the administration of an IV acetaminophen formulation to a patient. In some embodiments, a kit comprises a unit dosage form of an acetaminophen IV formulation as described herein provided as a sterile lyophilate to be reconstituted by addition of sterile water. In other embodiments, the IV formulation is provided as a sterile degassed solution ready for administration. The kit can further comprise a label or printed instructions on the use of the acetaminophen IV formulation to treat pain or fever. The kit can also further comprise a unit dosage form of another therapeutic agent, for example, a container containing an effective amount of a second analgesic agent for use in combination with the acetaminophen IV formulation. In some embodiments, a kit further comprises a device that is useful for administering the IV formulation unit dosage forms. Examples of such a device include, but are not limited to, a syringe or a drip bag.

While preferred embodiments of the present invention have been shown and described herein, it will be understood that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions can be made without departing from the scope of the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby. Thus, these examples should not be read as limiting the example in any way. For example, different amounts of the components described in the following examples as well as the components themselves can be changed according to the disclosure provided herein.

## EXAMPLES

### Example 1

### IV Acetaminophen Formulations

TABLE 1

| Exemplary IV Formulation of Acetaminophen | |
|---|---|
| Acetaminophen | 0.550 g-1.000 g |
| Excipients: | |
| Antioxidant | 0.0100-0.0200 g |
| pH modulator(s) | qs pH 5-6 |
| Buffer | 0.005-0.01 g |
| Isotonic Agent | 1.5-3.5 g |
| Solvent | qs 50.0-100.0 mL |

### Example 1A

### IV Acetaminophen Formulations

Example 1A is prepared according to the procedure outlined in Example 2 using the amounts of the excipients described in Example 1.

| Formula 1(A) | | | | | |
|---|---|---|---|---|---|
| | Acetaminophen | | | | |
| Excipients: | 0.550 g | 0.650 g | 0.750 g | 0.850 g | 0.950 g |
| Antioxidant | Reduced Glutathione | Reduced Glutathione | Reduced Glutathione | Reduced Glutathione | Reduced Glutathione |
| pH Modulator | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide |
| pH Modulator | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid |
| Buffering Agent | Sodium Citrate | Sodium Citrate | Sodium Citrate | Sodium Citrate | Sodium Citrate |

-continued

| Formula 1(A) | | | | | |
|---|---|---|---|---|---|
| | Acetaminophen | | | | |
| Excipients: | 0.550 g | 0.650 g | 0.750 g | 0.850 g | 0.950 g |
| Isotonicity Agent | Sodium Chloride | Sodium Chloride | Sodium Chloride | Sodium Chloride | Sodium Chloride |
| Solvent | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection |

Example 1B

IV Acetaminophen Formulations

Example 1B is prepared according to the procedure outlined in Example 2 using the amounts of the excipients described in Example 1.

| Formula 1(B) | | | | | |
|---|---|---|---|---|---|
| | Acetaminophen | | | | |
| Excipients: | 0.550 g | 0.650 g | 0.750 g | 0.850 g | 0.950 g |
| Antioxidant | Methionine | Methionine | Methionine | Methionine | Methionine |
| pH Modulator | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide |
| pH Modulator | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid |
| Buffering Agent | Sodium Acetate | Sodium Acetate | Sodium Acetate | Sodium Acetate | Sodium Acetate |
| Isotonicity Agent | Mannitol | Mannitol | Mannitol | Mannitol | Mannitol |
| Solvent | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection |

Example 1C

IV Acetaminophen Formulations

Example 1C is prepared according to the procedure outlined in Example 2 using the amounts of the excipients described in Example 1.

| Formula 1(C) | | | | | |
|---|---|---|---|---|---|
| | Acetaminophen | | | | |
| Excipients: | 0.550 g | 0.650 g | 0.750 g | 0.850 g | 0.950 g |
| Antioxidant | Cysteine Hydrocloride Monohydrate | Cysteine Hydrocloride Monohydrate | Cysteine Hydrocloride Monohydrate | Cysteine Hydrocloride Monohydrate | Cysteine Hydrocloride Monohydrate |
| pH Modulator | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide |
| pH Modulator | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid |
| Buffering Agent | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate |
| Isotonicity Agent | Mannitol | Mannitol | Mannitol | Mannitol | Mannitol |
| Solvent | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection |

Example 1D

IV Acetaminophen Formulations

Example 1D is prepared according to the procedure outlined in Example 2 using the amounts of the excipients described in Example 1.

Formula 1(D)

| | Acetaminophen | | | | |
|---|---|---|---|---|---|
| Excipients: | 0.550 g | 0.650 g | 0.750 g | 0.850 g | 0.950 g |
| Antioxidant | Ascorbic Acid | Ascorbic Acid | Ascorbic Acid | Ascorbic Acid | Ascorbic Acid |
| pH Modulator | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide |
| pH Modulator | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid |
| Buffering Agent | Sodium Tartate | Sodium Tartate | Sodium Tartate | Sodium Tartate | Sodium Tartate |
| Isotonicity Agent | Glycerol | Glycerol | Glycerol | Glycerol | Glycerol |
| Solvent | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection |

Example 1E

IV Acetaminophen Formulations

Example 1E is prepared according to the procedure outlined in Example 2 using the amounts of the excipients described in Example 1.

Formula 1(E)

| | Acetaminophen | | | | |
|---|---|---|---|---|---|
| Excipients: | 0.550 g | 0.650 g | 0.750 g | 0.850 g | 0.950 g |
| Antioxidant | Acetylcysteine | Acetylcysteine | Acetylcysteine | Acetylcysteine | Acetylcysteine |
| pH Modulator | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide |
| pH Modulator | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid |
| Buffering Agent | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate |
| Isotonicity Agent | Sorbitol | Sorbitol | Sorbitol | Sorbitol | Sorbitol |
| Solvent | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection |

Example 1F

IV Acetaminophen Formulations

Example 1F is prepared according to the procedure outlined in Example 2 using the amounts of the excipients described in Example 1.

Formula 1(F)

| | Acetaminophen | | | | |
|---|---|---|---|---|---|
| Excipients: | 0.550 g | 0.650 g | 0.750 g | 0.850 g | 0.950 g |
| Antioxidant | metabisulfite | metabisulfite | metabisulfite | metabisulfite | metabisulfite |
| pH Modulator | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide | Sodium hydroxide |
| pH Modulator | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid | Hydrochloric Acid |

-continued

| Formula 1(F) | | | | | |
|---|---|---|---|---|---|
| | Acetaminophen | | | | |
| Excipients: | 0.550 g | 0.650 g | 0.750 g | 0.850 g | 0.950 g |
| Buffering Agent | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate | Disodium Phosphate Dehydrate |
| Isotonicity Agent | Glucose | Glucose | Glucose | Glucose | Glucose |
| Solvent | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection | Sterile Water for injection |

Example 2

Preparation of IV Formulation Solutions

Prior to storage the formulations set forth in Example 1 are subjected to bubbling with nitrogen, transferred to Type II colorless bottles, and then placed under vacuum (low pressure approx. 550 mm of Hg) before stoppering the bottles with a synthetic elastomer grey stopper crimped with an aluminum cap. The residual oxygen content is approximately 1.5 ppm of dissolved oxygen. The bottles are then sterilized at 121° C. for 15 minutes. Sterile solutions are stored at ambient temperature (less than 30° C.) for up to two years prior to use.

Example 3

A Phase III Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel-Group, Repeated-Dose Study of the Analgesic Efficacy and Safety of 650 mg IV Acetaminophen Versus Placebo for the Treatment of Postoperative Pain After Abdominal Laparoscopic Surgery

In an effort to provide an intravenous, non-NSAID, non-opioid treatment for pain relief, the safety and efficacy of a 650 mg IV dose of APAP for the treatment of acute pain is examined.

Study Design and Evaluation

A Phase III, randomized, double-blind, Placebo-controlled, multi-center, parallel-group, repeated dose study is conducted in approximately 240 Subjects who have undergone planned or elective abdominal laparoscopic surgery. Approximately 15 to 20 US sites will participate in the Study.

Subjects will be centrally randomized, across all study centers, to receive infusions of Study Medication (either APAP or Placebo) at a dose at a dose (650 mg, 1000 mg, or placebo) and schedule described below.

Timed PI and pain relief (PR) Assessments will begin at baseline just prior to T0, the start of the first infusion of Study Medication, and continue through T24 hours.

All Subjects have access to rescue medication at all times throughout the study, as described below.

The Study will include the following assessment periods and procedures:

Screening (Day −21 to Randomization)

Screening is the period that begins when the Subject signs the Informed Consent Form and ends with randomization to Study Medication on POD1. During this period, the eligibility and baseline status of the Subject are determined.

Treatment Period (Dose 1/T0/POD1 to T24/POD2)

Administration of Study Medication (and Study-related assessments) will occur from T0 (morning of POD1) to T24 hours (morning of POD2).

Criteria for Evaluation

The primary efficacy endpoint is SPID24 (defined as the Sum of VAS score differences from baseline at T0 to T24), excluding all data after rescue medication.

Subject Selection Criteria

To be eligible for entry into the Study, Subjects must meet all of the following criteria prior to surgery: (1) Provide written Informed Consent prior to participation in the Study; (2) is scheduled to undergo abdominal laparoscopic surgery (laparoscopic gastric bypass procedures are not eligible); (3) If Subject is a female of childbearing potential, have a negative pregnancy test within 21 days of surgery; (4) be at least 18, but not more than 80 years of age; (5) Have a Body Mass Index (BMI)≥19 and ≤45 $lb/in^2$; (6) Have an ASA risk class of I, II, or III according to the American Society of Anesthesiologists; (7) Have the ability to read and understand the Study procedures and the use of the pain scales and have the ability to communicate meaningfully with the Study Investigator and staff; (8) Be free of other physical, mental, or medical conditions which, in the opinion of the Investigator, makes Study participation inadvisable

Exclusion Criteria (Screening)

A Subject is NOT eligible for entry if ANY of the following criteria are met: (1) Used opioids or tramadol daily for greater than 7 days prior to Study Medication administration (Subjects who, in the Investigator's opinion have or are developing opioid tolerance are to be excluded); (2) Has been treated with Chapparal, Comfrey, Germander, Gin Bu Huan, Kava, Pennyroyal, Skullcap, St. John's Wort, or Valerian within 14 days prior to surgery; (3) Has significant medical disease(s), laboratory abnormalities or condition(s) that in the Investigator's judgment could compromise the Subject's welfare, ability to communicate with the Study staff, complete Study activities, or would otherwise contraindicate Study participation; (4) Has known hypersensitivity to opioids, acetaminophen, or the inactive ingredients (excipients) of the Study Medication; (5) Has known or suspected history of alcohol or drug abuse or dependence within the previous 2 years; (6) Has impaired liver function, e.g., AST/ALT/bilirubin greater than or equal to 3.0 times the upper limit of normal, active hepatic disease, evidence of clinically significant liver disease, or other condition (e.g., alcoholism, cirrhosis, or hepatitis) that may suggest the potential for an increased susceptibility to hepatic toxicity with Study Medication exposure; (7) Has been treated with monoamine oxidase inhibitors (MAOIs) within 7 days prior to surgery; (8) Has participated in another clinical Study (investigational or marketed product) within 30 days of surgery

Post Operative Exclusion Criteria

The Subject must not meet any of the following criteria after surgery and prior to randomization to Study Medication: (1) Had any other surgery than the planned laparoscopic surgery or had intra operative or post operative complications

which in the view of the Investigator would make Study participation inadvisable; (2) Has taken non steroidal anti-inflammatory drugs (NSAIDs), steroids or MAOIs during the day after surgery. Exceptions: The use of low-dose aspirin, e.g., 81 mg/day, for cardioprophylaxis, and topical or inhaled steroids are acceptable; (3) Had any neuraxial opioids or continuous local anesthetic infusions via percutaneous catheters administered as part of the anesthetic or post operative analgesic management (local anesthetic infiltration of surgical wounds at the time of closure is acceptable if done as a single injection); (4) Had a fever (greater than 38.6° C. or 101.5° F.) requiring treatment.

Postoperative Assessment (POD0)

The Subject will undergo abdominal laparoscopic surgery or other approved surgical procedure as described herein. Details of the surgical procedure(s) will be recorded on the CRF including the type of procedure(s) performed and perioperative medication will be recorded.

## Example 4

### Phase III, Open-Label, Prospective, Multi-Center, Repeated Dose, Randomized, Multi-Day Safety and Efficacy Study of 650 mg IV Acetaminophen

A Phase III, open-label, prospective, multi-center, repeated dose, randomized, multi-day safety and efficacy study was conducted in 213 subjects. The subjects were randomized as follows: 92 subjects to a q6 group (1 g of IV acetaminophen every 6 hours), 91 subjects to a q4 group (650 mg of IV acetaminophen every 4 hours), and 28 subjects to a standard of care control group, which could include oral acetaminophen, but no IV acetaminophen. Subjects who completed 5 days of study treatment included 63 in the q6 group, 59 in the q4 group and 26 in the control group. The primary endpoint was an assessment of safety using spontaneous adverse event reporting and daily liver enzymes. Efficacy evaluations were also performed.

Inclusion Criteria (Screening)

To be eligible for entry into the Study, Subjects had to meet all the following criteria: (1) Provide written informed consent prior to participation in the Study; (2) Be at least 18 years of age and weigh at least 41 kg; (3) Be anticipated by the Investigator to require multi-day (target is five days) use of IV treatment either because of: (a) having a "nothing by mouth" (NPO) status, (b) having a medical condition that makes oral intake difficult, or (c) having a medical condition that requires IV treatment; (4) Be willing to undergo 5 days of treatment with IV acetaminophen for the treatment of pain or fever (defined as a core temperature ≥38° C.). Subjects had a slightly less than 15% chance (one in seven) of being assigned to the Control Group and receiving standard of care treatment, but no IV APAP; (5) Have the ability to read and understand the Study procedures and have the ability to communicate meaningfully with the Study Investigator and staff, and (6) If a female of child bearing potential, have a negative pregnancy test within 48 hours of randomization.

Exclusion Criteria (Screening)

A Subject was not eligible for entry if any of the following criteria were met: (1) Had a significant medical disease, laboratory abnormality or condition that, in the Investigator's judgment, could compromise the Subject's welfare or would otherwise contraindicate Study participation; (2) Was expected to have difficulty in communicating with the Study staff or completing Study requirements (including follow up visits); (3) Had known hypersensitivity to acetaminophen or the inactive ingredients (excipients) of IV acetaminophen or any contraindication to receiving acetaminophen; (4) Had impaired liver function, e.g., ALT greater than or equal to 3 times the upper limit of normal (ULN), bilirubin greater than or equal to 3 times ULN, known active hepatic disease (e.g., hepatitis), evidence of clinically significant chronic liver disease or other condition affecting the liver (e.g., alcoholism as defined by DSM-IV, cirrhosis or chronic hepatitis); or (5) Had participated in an interventional clinical Study (investigational or marketed product) within 30 days of Study entry.

Efficacy Analysis

All analyses of efficacy were conducted on the modified intent-to-treat population separately for the two indications (acute pain and fever). Subjects' Global Evaluations were summarized descriptively (m, mean, SD, median, minimum, and maximum) by treatment group for each study day and for overall assessments. Summary statistics were also provided for each site.

Comparisons of efficacy endpoints between the following pairs of treatment groups were investigated using two-sided tests at the 5% level of significance:

IV acetaminophen 1 g versus IV acetaminophen 650 mg

IV acetaminophen 1 g versus standard of care treatment

IV acetaminophen 650 mg versus standard of care treatment

A one-way analysis of variance (ANOVA) model with treatment group as the factor was used to test the treatment difference between these pairs. All groups were included in this analysis model. The p-values from the ANOVA model were presented along with the summary statistics.

Safety Analyses

All analyses of safety were conducted on the safety population.

Percentage of subjects withdrawn due to adverse event, percentage of subjects with adverse events (AEs) or serious adverse events (SAEs), and percentage of subjects with clinically meaningful changes in laboratory parameters were summarized.

All adverse events and serious adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 10.0. Additional analyses included displays of the number of subjects reporting at least one AE (incidence table), total number of episodes of each AE by body system and by severity, total number of episodes of each AE by body system, and by attribution. Liver function test abnormalities were graded using the Common Terminology Criteria for Adverse Events.

For each clinical laboratory parameter, descriptive statistics (m, mean, standard deviation, median, and range) were tabulated for baseline and final values. Change from baseline was tabulated for those subjects who had both baseline and final values. Liver function tests were also evaluated using values that were normalized to the upper limit of normal values for the local laboratory.

A shift table was prepared to present the shift in baseline clinical laboratory values that were clinically relevantly high or low at baseline and/or final measurement.

Descriptive statistics (m, mean, standard deviation, median, and range) were tabulated for changes in vital signs from baseline to final measurement.

Results

Disposition of Subjects

A total of 257 subjects were screened for study enrollment. Of the total screened, 44 were screen failures, and 213 were enrolled and randomized: 92 subjects in the q6 group, 91 subjects in the q4 group, and 28 subjects in the control group.

Subjects who completed 5 days of study treatment included 63 in the q6 group, 59 in the q4 group and 26 in the control group.

Subjects in the q4h group and q6h group were considered to be a Study Treatment Discontinuation/Early Termination if they received at least one dose of IV acetaminophen and discontinued study participation prior to completion of Day 5 treatments. Subjects in the control group were considered to be a Study Treatment Discontinuation/Early Termination if they discontinued at any time after T0, but prior to completion of Day 5 standard of care treatments.

Subjects who received at least one dose of IV acetaminophen and discontinued study participation prior to completing Day 5 treatments, but returned for the Last Study Visit were considered as "Partial Treatment Completers". Similarly, subjects in the control group who discontinued study participation prior to completing Day 5 standard of care treatments, but returned for the Last Study Visit were considered as "Partial Treatment Completers".

Subjects who completed Day 5 treatments (IV acetaminophen or standard of care) and procedures were characterized as a "Treatment Completer". A Treatment Completer who elected to discontinue study participation prior to the Last Study Visit was characterized as a Treatment Completer Early Termination.

Safety Outcome

There were no clinically relevant differences between the treatment groups in the frequency of serious, severe, related, or overall treatment emergent adverse events (TEAEs). In fact, most TEAEs were assessed by the Investigator to be mild or moderate in severity. The frequency of liver enzyme elevations seen in the treatment groups was comparable. More specifically, with regard to the hepatic transaminases alanine aminotransferase and aspartate aminotransferase, the frequency and severity of the elevations were comparable between the treatment groups. There were no clinically relevant differences between the treatment groups regarding laboratory assessments, vital signs, or physical examinations. Thus, based on these data, intravenous acetaminophen in both active treatment groups (i.e., 650 mg and 1000 mg dose groups) was well tolerated.

Efficacy Outcome

The modified intent-to-treat population was used for all analyses of efficacy: Subject Global Evaluations (rating of study treatments and rating of satisfaction with side effects related to study treatments) provided as a daily lookback (days 2 through 5) and overall evaluation (overall treatment period lookback) using a 4 point categorical rating scale (0=poor, 1=fair, 2=good, 3=excellent). A one-way ANOVA model with treatment group as the factor was used to test the treatment difference between each treatment pair:

- IV acetaminophen 1 g q6h versus IV acetaminophen 650 mg q4h
- IV acetaminophen 1 g q6h versus standard of care treatment (Control)
- IV acetaminophen 650 mg q4h versus standard of care treatment (Control)

All endpoints were tested at the 0.05 significance level (two-sided).

The IV acetaminophen 650 mg q4h group relative to the control group produced statistically significantly better satisfaction ratings for the Subject Global Assessments rating the level of satisfaction with the side effects related to study treatments the on the day 5 (mean rating 2.4 vs. 2.0, p=0.0167) and at the end of day 5 prior to discharge (mean rating 2.4 vs. 2.0, p=0.0129) 24 h look back assessments. On day 4, the satisfaction rating showed a trend to significance (mean rating 2.5 vs. 2.2, p=0.1162). With respect to the Subject Global Assessments rating the level of satisfaction with the study treatments, there were no statistically significant differences between the IV acetaminophen 650 mg q6h group and control group at any of the assessment points. For the both of the Subject Global Assessments rating either the level of satisfaction with the study treatments or the level of satisfaction with the side effects related to study treatments, there was no statistically significant differences between the two active treatment groups with respect to the daily 24 h lookback assessments on day 2, day 3, day 4, day 5, or at the end of day 5 prior to discharge; nor was there a statistically significant difference on the overall assessment at the Study Completion Visit.

The IV acetaminophen 1 g q6h group produced statistically significantly better satisfaction ratings for the Subject Global Assessments rating the level of satisfaction with the side effects related to study treatments on day 5 (mean rating 2.4 vs. 2.0, p=0.0062) and at the end of day 5 prior to discharge (mean rating 2.5 vs. 2.0, p=0.0073) 24 h lookback assessments compared to the control group. On day 4, the satisfaction rating showed a trend to significance (mean rating 2.5 vs. 2.2, p=0.0744). With respect to the Subject Global Assessments rating the level of satisfaction with the study treatments, there were no statistically significant differences between the IV acetaminophen 1 g q6h group and control group at any of the assessment points.

Statistically significant differences were observed for both active treatment groups versus the control group in the Subject Global Assessments rating the level of Satisfaction with the side effects related to study treatments on the day 5 and on the end of day 5 prior to discharge daily 24 h lookback assessments. Thus, these data suggest that the IV acetaminophen 1 g q6h and 650 mg q4h groups were efficacious and provided comparable efficacy based upon the global satisfaction ratings.

Many modifications, equivalents, and variations of the present invention are possible in light of the above teachings, therefore, it is to be understood that within the scope of the appended claims, the invention may be practiced other than as specifically described.

What is claimed is:

**1**. A method for the treatment of pain or fever in an adult human or an adolescent human subject weighing at least 50 kg, in need thereof, comprising administering to the subject, by an intravenous route of administration, a therapeutically effective amount of a pharmaceutical composition comprising about 550 mg to about 800 mg of acetaminophen; and repeating said administration at least once at an interval of about 3 to about 5 hours.

**2**. The method of claim **1**, wherein the subject receives a total of about 3 to about 5 grams of acetaminophen in a period of twenty four hours.

**3**. The method of claim **2**, wherein the pharmaceutical composition is administered at least six times in a period of twenty four hours.

**4**. The method of claim **1**, wherein the pharmaceutical composition comprises at least one antioxidant.

**5**. The method of claim **4**, wherein the at least one antioxidant is selected from the group consisting of cysteine hydrochloride monohydrate, thiolyglycolic acid, thiolacetic acid, dithiothreitol, reduced glutathione, thiourea, a-thioglycerol, cysteine, aceticysteine, mercaptoethane sulfonic acid, ascorbic acid, ascorbic acid derivatives, an organic compound having at least one thiol, an alkyl polyhydroxylated compound, a cycloalkyl polyhydroxylated compound, and mixtures thereof.

6. The method of claim 5, wherein the at least one antioxidant comprises cysteine hydrochloride monohydrate.

7. The method of claim 1, further comprising a buffering agent.

8. The method of claim 7, wherein the buffering agent comprises disodium phosphate dehydrate.

9. The method of claim 1, wherein the pharmaceutical composition has a pH between about 4 to about 8.

10. The method of claim 9, wherein the pharmaceutical composition has a pH of between about 5 and about 6.

11. The method of claim 1, wherein the pharmaceutical composition has an osmolality of between about 200 mOsm/L to about 400 mOsm/L.

12. The pharmaceutical composition of claim 11, wherein the acetaminophen is present in the composition in an amount of about 600 mg to about 700 mg.

13. The method of claim 1, wherein the pharmaceutical composition further comprises an isotonicity agent.

14. The method of claim 13, wherein the isotonicity agent is dextrose, mannitol, or lactose.

15. The method of claim 14, wherein the isotonicity agent is mannitol.

16. The method of claim 1, further comprising EDTA.

17. The method of claim 1, wherein the pharmaceutical composition further comprises at least one analgesic agent other than acetaminophen.

18. The method of claim 17, wherein the at least one analgesic agent other than acetaminophen comprises an anilide, an opioid, an NSAID, a cannabinoid, a pyrazalone, or a barbiturate.

19. The method of claim 18, wherein the at least one analgesic agent other than acetaminophen comprises an opioid.

20. The method of claim 1, wherein the subject is suffering from a fever.

21. The method of claim 1, wherein the subject is unconscious, sedated, fasting, nauseous, or unable to be administered a pharmaceutical composition by an oral route.

22. The method of claim 1, wherein the pharmaceutical composition is administered after a surgical intervention on the subject.

23. The method of claim 1, wherein the pharmaceutical composition is administered within 3 hours of a surgical intervention on the subject.

24. The method of claim 23, wherein the pharmaceutical composition is administered within 1 hour of a surgical intervention on the subject.

25. The method of claim 1, wherein the pharmaceutical composition is administered postoperatively.

26. The method of claim 1, further comprising administering to the subject at least one analgesic agent other than acetaminophen.

27. The method of claim 26, wherein the at least one analgesic agent other than acetaminophen comprises an anilide, an opioid, an NSAID, a cannabinoid, a pyrazalone, or a barbiturate.

28. The method of claim 1, wherein the subject is suffering from an infection.

29. A method for reducing pain or fever in an adult human or an adolescent human subject weighing at least 50 kg, in need thereof, comprising administering to the subject, by an intravenous route of administration, a therapeutically effective amount of a pharmaceutical composition in solution comprising: about 600 mg to about 700 mg of acetaminophen, cysteine hydrochloride monohydrate, disodium phosphate dehydrate, and mannitol, wherein the solution has a pH of about 5 to about 6, and an osmolality of about 200-400 mOsm/L; and repeating said administration at least once at an interval of about 3 to about 5 hours.

30. The method of claim 29, wherein the pharmaceutical composition has an acetaminophen concentration of about 0.5% (w/v) to about 10% (w/v).

31. The method of claim 30, wherein the acetaminophen concentration is about 1% (w/v).

32. The method of claim 29, wherein the pharmaceutical composition further comprises EDTA.

33. The method of claim 29, wherein the subject is suffering from postoperative pain.

34. The method of claim 1, wherein the level of pain the subject is suffering from is reduced.

35. The method of claim 1, wherein the pharmaceutical composition is administered as a pretreatment.

36. The method of claim 29, wherein the administered dose of acetaminophen is 650 mg, and further comprising repeating intravenous administration of 650 mg acetaminophen at least once at an interval of about 3 hours to about 5 hours.

37. The method of claim 36, wherein the interval is about 4 hours.

38. The method of claim 1, further comprising repeating intravenous administration of about 600 mg to about 700 mg acetaminophen at least once at an interval of about 3 hours to about 5 hours.

39. The method of claim 1, wherein the administered dose of acetaminophen is 650 mg, and further comprising repeating intravenous administration of 650 mg acetaminophen at least once at an interval of about 3 hours to about 5 hours.

40. The method of claim 29, wherein the interval is about 4 hours.

41. The method of claim 1, wherein the composition may be administered to the subject without dilution.

42. The method of claim 1, wherein the composition is a sterile solution that is ready for direct administration to the subject.

43. The method of claim 1, wherein the pharmaceutical composition is a lyophilized powder.

44. The method of claim 43, wherein the lyophilized powder must be reconstituted in solution prior to administration.

45. The method of claim 1, wherein the pharmaceutical composition is intravenously administered to the subject over about 5 minutes to about 30 minutes.

46. The method of claim 45, wherein the pharmaceutical composition is intravenously administered to the subject over about 15 minutes.

47. The method of claim 1, wherein the subject is administered less than 4 grams of acetaminophen over a twenty-four hour period.

48. A method of treating pain in a human subject weighing at least 50 kg comprising:

administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising about 600 mg to about 700 mg of acetaminophen; and

repeating said administration at least about once every 4 hours;

wherein the composition is administered to the subject as a 15-minute intravenous infusion, and

wherein the subject is administered less than 4 grams of acetaminophen over a 24-hour period.

49. The method of claim 48, wherein the composition comprises about 650 mg of acetaminophen.

50. The method of claim 48, wherein the composition is administered to the subject at least six times in a period of 24 hours.

**51**. The method of claim **48**, wherein the composition is administered to the subject at least seven times in a period of 24 hours.

**52**. The method of claim **48**, wherein the composition is administered to the subject at least eight times in a period of 24 hours.

**53**. The method of claim **48**, wherein the composition may be administered to the subject without dilution.

**54**. The method of claim **48**, wherein the composition is a sterile solution that is ready for subject administration.

**55**. The method of claim **48**, wherein the composition is a lyophilized powder.

**56**. The method of claim **55**, wherein the lyophilized powder must be reconstituted in solution prior to subject administration.

**57**. The method of claim **48**, wherein the composition may be stored at ambient temperature for two years prior to use.

**58**. The method of claim **57**, wherein the ambient temperature is less than 30 degrees Celsius.

**59**. The method of claim **48**, wherein the composition further comprises a buffer in an amount of about 0.1% to about 0.7%.

**60**. The method of claim **48**, wherein the composition further comprises a buffer in an amount of about 0.2% to about 0.3%.

**61**. The method of claim **48**, wherein the composition further comprises a buffer in an amount of about 0.05% to about 2.0%.

**62**. The method of claim **48**, wherein the composition further comprises at least one buffering agent.

**63**. The method of claim **62**, wherein the at least one buffering agent is selected from the group consisting of a pharmaceutically acceptable salt or acid of citrate, phosphate, acetate, glutamate, tartrate, benzoate, lactate, histidine or other amino acids, gluconate, malate, succinate, formate, propionate, carbonate, or any combination thereof.

**64**. The method of claim **63**, wherein the at least one buffering agent is disodium phosphate dehydrate.

**65**. The method of claim **48**, wherein the pharmaceutical composition has a pH between about 4 to about 8.

**66**. The method of claim **48**, wherein the pharmaceutical composition has a pH of between about 5 and about 6.

**67**. The method of claim **48**, wherein the composition further comprises an antioxidant in an amount of about 0.3% to about 1.0%.

**68**. The method of claim **48**, wherein the composition further comprises an antioxidant in an amount of about 0.5%.

**69**. The method of claim **48**, wherein the composition further comprises at least one antioxidant.

**70**. The method of claim **69**, wherein the at least one antioxidant is selected from the group consisting of cysteine hydrochloride monohydrate, thiolyglycolic acid, thiolacetic acid, dithiothreitol, reduced glutathione, thiourea, a-thioglycerol, cysteine, aceticysteine, mannitol, mercaptoethane sulfonic acid, ascorbic acid, ascorbic acid derivatives, an organic compound having at least one thiol, an alkyl polyhydroxylated compound, a cycloalkyl polyhydroxylated compound, and mixtures thereof.

**71**. The method of claim **70**, wherein the at least one antioxidant is cysteine hydrochloride monohydrate.

**72**. The method of claim **70**, wherein the at least one antioxidant is mannitol.

**73**. The method of claim **48**, wherein the composition further comprises an isotonicity agent in an amount of about 65% to about 85%.

**74**. The method of claim **48**, wherein the composition further comprises at least one isotonicity agent.

**75**. The method of claim **74**, wherein the at least one isotonicity agent is selected from the group consisting of mannitol, sorbitol, glycerol, sucrose, glucose, dextrose, levulose, fructose, lactose, polyethylene glycols 400 to 4000, phosphates, sodium chloride, potassium chloride, calcium chloride, calcium gluconoglucoheptonate, dimethyl sulfone, and combinations thereof.

**76**. The method of claim **75**, wherein the at least one isotonicity agent is mannitol.

**77**. The method of claim **48**, wherein the composition has an osmolality of between about 200 mOsm/L to about 400 mOsm/L.

**78**. The method of claim **48**, wherein the composition comprises 650 mg of acetaminophen, and wherein the subject is administered the composition every four hours in a twenty-four hour period.

**79**. A method of reducing fever in a human subject weighing at least 50 kg comprising:

administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising about 600 mg to about 700 mg of acetaminophen; and

repeating said administration at least about once every 4 hours;

wherein the composition is administered to the subject as a 15-minute intravenous infusion, and

wherein the subject is administered less than 4 grams of acetaminophen over a twenty-four hour period.

**80**. The method of claim **79**, wherein the composition comprises about 650 mg of acetaminophen.

**81**. The method of claim **79**, wherein the composition is administered to the subject at least six times in a period of 24 hours.

**82**. The method of claim **79**, wherein the composition is administered to the subject at least seven times in a period of 24 hours.

**83**. The method of claim **79**, wherein the composition is administered to the subject at least eight times in a period of 24 hours.

**84**. The method of claim **79**, wherein the composition may be administered to the subject without dilution.

**85**. The method of claim **79**, wherein the composition is a sterile solution that is ready for subject administration.

**86**. The method of claim **79**, wherein the composition is a lyophilized powder.

**87**. The method of claim **86**, wherein the lyophilized powder must be reconstituted in solution prior to administration.

**88**. The method of claim **79**, wherein the composition may be stored at ambient temperature for two years prior to use.

**89**. The method of claim **88**, wherein the ambient temperature is less than 30 degrees Celsius.

**90**. The method of claim **79**, wherein the composition further comprises a buffer in an amount of about 0.1% to about 0.7%.

**91**. The method of claim **79**, wherein the composition further comprises a buffer in an amount of about 0.2% to about 0.3%.

**92**. The method of claim **79**, wherein the composition further comprises a buffer in an amount of about 0.05% to about 2.0%.

**93**. The method of claim **79**, wherein the composition further comprises at least one buffering agent.

**94**. The method of claim **93**, wherein the at least one buffering agent is selected from the group consisting of a pharmaceutically acceptable salt or acid of citrate, phosphate, acetate, glutamate, tartrate, benzoate, lactate, histidine or other amino acids, gluconate, malate, succinate, formate, propionate, carbonate, or any combination thereof.

**95**. The method of claim **94**, wherein the at least one buffering agent is disodium phosphate dehydrate.

**96**. The method of claim **79**, wherein the pharmaceutical composition has a pH between about 4 to about 8.

**97**. The method of claim **79**, wherein the pharmaceutical composition has a pH of between about 5 and about 6.

**98**. The method of claim **79**, wherein the composition further comprises an antioxidant in an amount of about 0.3% to about 1.0%.

**99**. The method of claim **79**, wherein the composition further comprises an antioxidant in an amount of about 0.5%.

**100**. The method of claim **79**, wherein the composition further comprises at least one antioxidant.

**101**. The method of claim **100**, wherein the at least one antioxidant is selected from the group consisting of cysteine hydrochloride monohydrate, thiolyglycolic acid, thiolacetic acid, dithiothreitol, reduced glutathione, thiourea, a-thioglycerol, cysteine, aceticysteine, mannitol, mercaptoethane sulfonic acid, ascorbic acid, ascorbic acid derivatives, an organic compound having at least one thiol, an alkyl polyhydroxylated compound, a cycloalkyl polyhydroxylated compound, and mixtures thereof.

**102**. The method of claim **101**, wherein the at least one antioxidant is cysteine hydrochloride monohydrate.

**103**. The method of claim **101**, wherein the at least one antioxidant is mannitol.

**104**. The method of claim **79**, wherein the composition further comprises an isotonicity agent in an amount of about 65% to about 85%.

**105**. The method of claim **79**, wherein the composition further comprises at least one isotonicity agent.

**106**. The method of claim **105**, wherein the at least one isotonicity agent is selected from the group consisting of mannitol, sorbitol, glycerol, sucrose, glucose, dextrose, levulose, fructose, lactose, polyethylene glycols 400 to 4000, phosphates, sodium chloride, potassium chloride, calcium chloride, calcium gluconoglucoheptonate, dimethyl sulfone, and combinations thereof.

**107**. The method of claim **106**, wherein the at least one isotonicity agent is mannitol.

**108**. The method of claim **79**, wherein the composition has an osmolality of between about 200 mOsm/L to about 400 mOsm/L.

**109**. The method of claim **79**, wherein the pharmaceutical composition comprises 650 mg of acetaminophen, and wherein the subject is administered the composition every four hours in a twenty-four hour period.

* * * * *

# EXHIBIT C

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use OFIRMEV® safely and effectively. See full prescribing information for OFIRMEV.**

**OFIRMEV (acetaminophen) Injection**
**Initial U.S. Approval: 1951**

**WARNING: RISK OF MEDICATION ERRORS AND HEPATOTOXICITY**

***See full prescribing information for complete boxed warning***

**Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death.**

**OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the recommended maximum daily limits, and often involve more than one acetaminophen-containing product (see WARNINGS).**

## RECENT MAJOR CHANGES

| | |
|---|---|
| Boxed Warning | 10/2013 |
| Dosage and Administration | |
| General Dosing Information (2.1) | 10/2013 |
| Recommended Dosage: Adults and Adolescents (2.2) | 10/2013 |
| Recommended Dosage: Children (2.3) | 10/2013 |
| Warnings and Precautions | |
| Hepatic Injury (5.1) | 10/2013 |
| Serious Skin Reactions (5.2) | 10/2013 |
| Risk of Medication Errors (5.3) | 10/2013 |

## INDICATIONS AND USAGE

OFIRMEV (acetaminophen) injection is indicated for the

- Management of mild to moderate pain (1)
- Management of moderate to severe pain with adjunctive opioid analgesics (1)
- Reduction of fever (1)

## DOSAGE AND ADMINISTRATION

- OFIRMEV may be given as a single or repeated dose. (2.1)
- OFIRMEV should be administered only as a 15-minute intravenous infusion. (2.4)

**Adults and Adolescents Weighing 50 kg and Over:**
- 1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day. Minimum dosing interval of 4 hours. (2.2)

**Adults and Adolescents Weighing Under 50 kg:**
- 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.2)

**Children:**
- Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.3)

## DOSAGE FORMS AND STRENGTHS

- Injection for intravenous infusion.
- Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL). (3)

## CONTRAINDICATIONS

Acetaminophen is contraindicated:
- In patients with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation. (4)
- In patients with severe hepatic impairment or severe active liver disease. (4)

## WARNINGS AND PRECAUTIONS

- Administration of acetaminophen in doses higher than recommended (by all routes of administration and from all acetaminophen-containing products including combination products) may result in hepatic injury, including the risk of liver failure and death. (5.1)
- Do not exceed the maximum recommended daily dose of acetaminophen (by all routes of administration and all acetaminophen-containing products including combination products). (5.1)
- Take care when prescribing, preparing, and administering OFIRMEV injection to avoid dosing errors which could result in accidental overdose and death. (5.3)
- Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, in cases of alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance ≤ 30 mL/min). (5.1)
- Discontinue OFIRMEV immediately at the first appearance of skin rash and if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy. (5.2, 5.4)

## ADVERSE REACTIONS

The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Cadence Pharmaceuticals Inc. at 1-877-647-2239 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

## DRUG INTERACTIONS

- Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. (7.1)
- Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. (7.2)

## USE IN SPECIFIC POPULATIONS

- Pregnancy: Category C. There are no studies of intravenous acetaminophen in pregnant women. Use only if clearly needed. (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Pediatric Use: The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients less than 2 years of age. The safety and effectiveness of OFIRMEV in pediatric patients older than 2 years is supported by evidence from adequate and well controlled studies in adults with additional safety and pharmacokinetic data for this age group. (8.4)
- Geriatric Use: No overall differences in safety or effectiveness were observed between geriatric and younger subjects. (8.5)
- Hepatic Impairment: OFIRMEV is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. (4, 5.1, 8.6)
- Renal Impairment: In cases of severe renal impairment, longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted. (5.1, 8.7)

**Revised: 10/2013**

FULL PRESCRIBING INFORMATION: CONTENTS*



*Sections or subsections omitted from the full prescribing information are not listed.

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# FULL PRESCRIBING INFORMATION

## WARNING: Risk of Medication Errors and Hepatotoxicity

Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:

- the dose in milligrams (mg) and milliliters (mL) is not confused;
- the dosing is based on weight for patients under 50 kg;
- infusion pumps are properly programmed; and
- the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.

OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limits, and often involve more than one acetaminophen-containing product (see WARNINGS).

## 1 INDICATIONS AND USAGE

OFIRMEV® (acetaminophen) injection is indicated for

- the management of mild to moderate pain
- the management of moderate to severe pain with adjunctive opioid analgesics
- the reduction of fever.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Dosing Information

OFIRMEV may be given as a single or repeated dose for the treatment of acute pain or fever. No dose adjustment is required when converting between oral acetaminophen and OFIRMEV dosing in adults and adolescents who weigh 50 kg and above. Calculated maximum daily dose of acetaminophen is based on all routes of administration (i.e., intravenous, oral, and rectal) and all products containing acetaminophen. Exceeding the maximum mg/kg daily dose of acetaminophen as described in Tables 1 and 2 may result in hepatic injury, including the risk of liver failure and death. To avoid the risk of overdose, ensure that the total amount of acetaminophen from all routes and from all sources does not exceed the maximum recommended dose.

### 2.2 Recommended Dosage: Adults and Adolescents

Adults and adolescents weighing 50 kg and over: the recommended dosage of OFIRMEV is 1000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of OFIRMEV of 1000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4000 mg per day (includes all routes of administration and all acetaminophen-containing products including combination products).

Adults and adolescents weighing under 50 kg: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of OFIRMEV of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day (includes all routes of administration and all acetaminophen-containing products including combination products).

**Table 1. Dosing for Adults and Adolescents**

| Age group | Dose given every 4 hours | Dose given every 6 hours | Maximum single dose | Maximum total daily dose of acetaminophen (by all routes) |
|---|---|---|---|---|
| **Adults and adolescents (13 years and older) weighing ≥ 50 kg** | 650 mg | 1000 mg | 1000 mg | 4000 mg in 24 hours |
| **Adults and adolescents (13 years and older) weighing < 50 kg** | 12.5 mg/kg | 15 mg/kg | 15 mg/kg (up to 750 mg) | 75 mg/kg in 24 hours (up to 3750 mg) |

**2.3 Recommended Dosage: Children**

Children 2 to 12 years of age: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of OFIRMEV of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.

**Table 2. Dosing for Children**

| Age group | Dose given every 4 hours | Dose given every 6 hours | Maximum single dose | Maximum total daily dose of acetaminophen (by all routes) |
|---|---|---|---|---|
| **Children 2 to 12 years of age** | 12.5 mg/kg | 15 mg/kg | 15 mg/kg (up to 750 mg) | 75 mg/kg in 24 hours (up to 3750 mg) |

**2.4 Instructions for Intravenous Administration**

For adult and adolescent patients weighing ≥ 50 kg requiring 1000 mg doses of OFIRMEV, administer the dose by inserting a vented intravenous set through the septum of the 100 mL vial. OFIRMEV may be administered without further dilution. Examine the vial contents before dose preparation or administering. DO NOT USE if particulate matter or discoloration is observed. Administer the contents of the vial intravenously over 15-minutes. Use aseptic technique when preparing OFIRMEV for intravenous infusion. Do not add other medications to the OFIRMEV vial or infusion device.

**For doses less than 1000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate container prior to administration.** Using aseptic technique, withdraw the appropriate dose (650 mg or weight-based) from an intact sealed OFIRMEV vial and place the measured dose in a separate empty, sterile container (e.g. glass bottle, plastic intravenous container, or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container. The entire 100 mL vial of OFIRMEV is not intended for use in patients weighing less than 50 kg. OFIRMEV is a single-use vial and the unused portion must be discarded.

Place small volume pediatric doses up to 60 mL in volume in a syringe and administer over 15 minutes using a syringe pump.

Monitor the end of the infusion in order to prevent the possibility of an air embolism, especially in cases where the OFIRMEV infusion is the primary infusion.

Once the vacuum seal of the glass vial has been penetrated, or the contents transferred to another container, administer the dose of OFIRMEV within 6 hours.

Do not add other medications to the OFIRMEV solution. Diazepam and chlorpromazine hydrochloride are physically incompatible with OFIRMEV, therefore do not administer simultaneously.

## 3 DOSAGE FORMS AND STRENGTHS

OFIRMEV is a sterile, clear, colorless, non pyrogenic, preservative free, isotonic formulation of acetaminophen intended for intravenous infusion. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL).

## 4 CONTRAINDICATIONS

Acetaminophen is contraindicated:

- in patients with known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation.
- in patients with severe hepatic impairment or severe active liver disease [*see WARNINGS AND PRECAUTIONS (5.1)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hepatic Injury

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death [*see OVERDOSAGE (10)*]. Do not exceed the maximum recommended daily dose of acetaminophen [*see DOSAGE AND ADMINISTRATION (2)*]. The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products.

Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min) [*see USE IN SPECIFIC POPULATIONS (8.6, 8.7)*].

### 5.2 Serious Skin Reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

### 5.3 Risk of Medication Errors

Take care when prescribing, preparing, and administering OFIRMEV (acetaminophen) Injection in order to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:

- the dose in milligrams (mg) and milliliters (mL) is not confused;
- the dosing is based on weight for patients under 50 kg;
- infusion pumps are properly programmed; and
- the total daily dose of acetaminophen from all sources does not exceed maximum daily limits [see *DOSAGE AND ADMINISTRATION (2)*].

### 5.4 Allergy and Hypersensitivity

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. There were infrequent reports of life-threatening anaphylaxis requiring emergent medical attention. Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use OFIRMEV in patients with acetaminophen allergy.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hepatic Injury [*see WARNINGS AND PRECAUTIONS (5.1)*]
- Serious Skin Reactions [*see WARNINGS AND PRECAUTIONS (5.2)*]
- Allergy and Hypersensitivity [*see WARNINGS AND PRECAUTIONS (5.4)*]

**6.1 Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

**Adult Population**

A total of 1020 adult patients have received OFIRMEV in clinical trials, including 37.3% (n=380) who received 5 or more doses, and 17.0% (n=173) who received more than 10 doses. Most patients were treated with OFIRMEV 1000 mg every 6 hours. A total of 13.1% (n=134) received OFIRMEV 650 mg every 4 hours.

All adverse reactions that occurred in adult patients treated with either OFIRMEV or placebo in repeated dose, placebo-controlled clinical trials at an incidence ≥ 3% and at a greater frequency than placebo are listed in Table 3. The most common adverse events in adult patients treated with OFIRMEV (incidence ≥ 5% and greater than placebo) were nausea, vomiting, headache, and insomnia.

**Table 3. Treatment-Emergent Adverse Reactions Occurring ≥ 3% in OFIRMEV-treated Patients and at a greater frequency than Placebo in Placebo-Controlled, Repeated Dose Studies**

| System Organ Class – Preferred Term | OFIRMEV (N=402) n (%) | Placebo (N=379) n (%) |
|---|---|---|
| **Gastrointestinal Disorders** | | |
| Nausea | 138 (34) | 119 (31) |
| Vomiting | 62 (15) | 42 (11) |
| **General Disorders and Administration Site Conditions** | | |
| Pyrexia* | 22 (5) | 52 (14) |
| **Nervous System Disorders** | | |
| Headache | 39 (10) | 33 (9) |
| **Psychiatric Disorders** | | |
| Insomnia | 30 (7) | 21 (5) |

* Pyrexia adverse reaction frequency data is included in order to alert healthcare practitioners that the antipyretic effects of OFIRMEV may mask fever.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Adults

The following additional treatment-emergent adverse reactions were reported by adult subjects treated with OFIRMEV in all clinical trials (n=1020) that occurred with an incidence of at least 1% and at a frequency greater than placebo (n=525).

Blood and lymphatic system disorders: anemia

General disorders and administration site conditions: fatigue, infusion site pain, edema peripheral

Investigations: aspartate aminotransferase increased, breath sounds abnormal

Metabolism and nutrition disorders: hypokalemia

Musculoskeletal and connective tissue disorders: muscle spasms, trismus

Psychiatric disorders: anxiety

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: hypertension, hypotension

**Pediatric population**

A total of 355 pediatric patients (47 neonates, 64 infants, 171 children, and 73 adolescents) have received OFIRMEV in active-controlled (n=250) and open-label clinical trials (n=225), including 59.7% (n=212) who received 5 or more doses and 43.1% (n=153) who received more than 10 doses. Pediatric patients received OFIRMEV doses up to 15 mg/kg on an every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

The most common adverse events (incidence ≥ 5%) in pediatric patients treated with OFIRMEV were nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Pediatrics

The following additional treatment-emergent adverse reactions were reported by pediatric subjects treated with OFIRMEV (n=355) that occurred with an incidence of at least 1%.

Blood and lymphatic system disorders: anemia
Cardiac disorders: tachycardia
Gastrointestinal disorders: abdominal pain, diarrhea
General disorders and administration site conditions: injection site pain, edema peripheral, pyrexia
Investigations: hepatic enzyme increase
Metabolism and nutrition disorders: hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypervolemia
Musculoskeletal and connective tissue disorders: muscle spasm, pain in extremity
Nervous system disorders: headache
Psychiatric disorders: insomnia
Renal and urinary disorders: oliguria
Respiratory, thoracic and mediastinal disorders: pulmonary edema, hypoxia, pleural effusion, stridor, wheezing
Skin and subcutaneous tissue disorders: periorbital edema, rash
Vascular disorders: hypertension, hypotension

## 7 DRUG INTERACTIONS

### 7.1 Effects of other Substances on Acetaminophen

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

### 7.2 Anticoagulants

Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of OFIRMEV in patients on oral anticoagulants, more frequent assessment of INR may be appropriate in such circumstances.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. There are no studies of intravenous acetaminophen in pregnant women; however, epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with IV acetaminophen, and it is not known whether OFIRMEV can cause fetal harm when administered to a pregnant woman. OFIRMEV should be given to a pregnant woman only if clearly needed.

The results from a large population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results.

While animal reproduction studies have not been conducted with intravenous acetaminophen, studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of

fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

**8.2 Labor and Delivery**

There are no adequate and well-controlled studies with OFIRMEV during labor and delivery; therefore, it should be used in such settings only after a careful benefit-risk assessment.

**8.3 Nursing Mothers**

While studies with OFIRMEV have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1 – 2% of the maternal dose. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use. Caution should be exercised when OFIRMEV is administered to a nursing woman.

**8.4 Pediatric Use**

The safety and effectiveness of OFIRMEV for the treatment of acute pain and fever in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. Additional safety and pharmacokinetic data were collected in 355 patients across the full pediatric age strata, from premature neonates (≥ 32 weeks post menstrual age) to adolescents. The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age. [*see DOSAGE AND ADMINISTRATION - Recommended Dosage: Children (2.3) and PHARMACOKINETICS (12.3)*].

**8.5 Geriatric Use**

Of the total number of subjects in clinical studies of OFIRMEV, 15% were age 65 and over, while 5% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**8.6 Patients with Hepatic Impairment**

Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease [*see WARNINGS AND PRECAUTIONS (5.1), CLINICAL PHARMACOLOGY (12)*]. A reduced total daily dose of acetaminophen may be warranted.

**8.7 Patients with Renal Impairment**

In cases of severe renal impairment (creatinine clearance ≤ 30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted.

**10 OVERDOSAGE**

Signs and Symptoms

In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in

90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

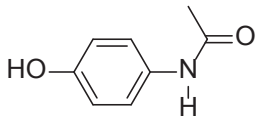
Treatment

If an acetaminophen overdose is suspected, obtain a serum acetaminophen assay as soon as possible, but no sooner than 4 hours following oral ingestion. Obtain liver function studies initially and repeat at 24-hour intervals. Administer the antidote N-acetylcysteine (NAC) as early as possible. As a guide to treatment of acute ingestion, the acetaminophen level can be plotted against time since oral ingestion on a nomogram (Rumack-Matthew). The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line, administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower line.

For additional information, call a poison control center at 1-800-222-1222.

## 11 DESCRIPTION

Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent. Its chemical name is N-acetyl-p-aminophenol. Acetaminophen has a molecular weight of 151.16. Its structural formula is:




OFIRMEV injection is a sterile, clear, colorless, non pyrogenic, isotonic formulation of acetaminophen intended for intravenous infusion. It has a pH of approximately 5.5 and an osmolality of approximately 290 mOsm/kg. Each 100 mL contains 1000 mg acetaminophen, USP, 3850 mg mannitol, USP, 25 mg cysteine hydrochloride, monohydrate, USP, 10.4 mg dibasic sodium phosphate, USP. pH is adjusted with hydrochloric acid and/or sodium hydroxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The precise mechanism of the analgesic and antipyretic properties of acetaminophen is not established but is thought to primarily involve central actions.

### 12.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies.

Single doses of OFIRMEV up to 3000 mg and repeated doses of 1000 mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation. Acetaminophen does not have any immediate or delayed effects on small-vessel hemostasis. Clinical studies of both healthy subjects and patients with hemophilia showed no significant changes in bleeding time after receiving multiple doses of oral acetaminophen.

### 12.3 Pharmacokinetics

Distribution

The pharmacokinetics of OFIRMEV have been studied in patients and healthy subjects from premature neonates up to adults 60 years old. The pharmacokinetic profile of OFIRMEV has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1000 mg.

The maximum concentration ($C_{max}$) occurs at the end of the 15 minute intravenous infusion of OFIRMEV. Compared to the same dose of oral acetaminophen, the $C_{max}$ following administration of OFIRMEV is up to 70% higher, while overall exposure (area under the concentration time curve [AUC]) is very similar.

Pharmacokinetic parameters of OFIRMEV (AUC, $C_{max}$, terminal elimination half-life [$T_{½}$], systemic clearance [CL], and volume of distribution at steady state [Vss]) following administration of a single intravenous dose of 15 mg/kg for the pediatric population and 1000 mg in adults are summarized in Table 4.

**Table 4. OFIRMEV Pharmacokinetic Parameters**

| Subpopulations | Mean (SD) | | | | |
|---|---|---|---|---|---|
| | AUC (µg × h/mL) | $C_{max}$ (µg/mL) | $T_{½}$ (h) | CL (L/h/kg) | Vss (L/kg) |
| **Neonates** | 62 (11) | 25 (4) | 7.0 (2.7) | 0.12 (0.04) | 1.1 (0.2) |
| **Infants** | 57 (54) | 29 (24) | 4.2 ( 2.9) | 0.29 (0.15) | 1.1 (0.3) |
| **Children** | 38 (8) | 29 (7) | 3.0 (1.5) | 0.34 (0.10) | 1.2 (0.3) |
| **Adolescents** | 41 (7) | 31 (9) | 2.9 (0.7) | 0.29 (0.08) | 1.1 (0.3) |
| **Adults** | 43 (11) | 28 (21) | 2.4 (0.6) | 0.27 (0.08) | 0.8 (0.2) |

The pharmacokinetic exposure of OFIRMEV observed in children and adolescents is similar to adults, but higher in neonates and infants. Dosing simulations from pharmacokinetic data in infants and neonates suggest that dose reductions of 33% in infants 1 month to < 2 years of age, and 50% in neonates up to 28 days, with a minimum dosing interval of 6 hours, will produce a pharmacokinetic exposure similar to that observed in children age 2 years and older.

At therapeutic levels, binding of acetaminophen to plasma proteins is low (ranging from 10% to 25%). Acetaminophen appears to be widely distributed throughout most body tissues except fat.

Metabolism and Excretion

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: Conjugation with glucuronide, conjugation with sulfate, and oxidation via the cytochrome P450 enzyme pathway, primarily CYP2E1, to form a reactive intermediate metabolite (N-acetyl-p-benzoquinone imine or NAPQI). With therapeutic doses, NAPQI undergoes rapid conjugation with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates.

Acetaminophen metabolites are mainly excreted in the urine. Less than 5% is excreted in the urine as unconjugated (free) acetaminophen and more than 90% of the administered dose is excreted within 24 hours.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice (1.2-1.4 times the MHDD, based on a body surface area comparison).

Mutagenesis

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosomal aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Impairment of fertility

In studies conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there

was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

## 14 CLINICAL STUDIES

### 14.1 Adult Acute Pain

The efficacy of OFIRMEV in the treatment of acute pain in adults was evaluated in two randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain.

**Pain Study 1** evaluated the analgesic efficacy of repeated doses of OFIRMEV l000 mg vs. placebo every 6 hours for 24 hours in 101 patients with moderate to severe pain following total hip or knee replacement. OFIRMEV was statistically superior to placebo for reduction in pain intensity over 24 hours. There was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated.

**Pain Study 2** evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg every 6 hours or 650 mg every 4 hours for 24 hours versus placebo in the treatment of 244 patients with moderate to severe postoperative pain after abdominal laparoscopic surgery. Patients receiving OFIRMEV experienced a statistically significant greater reduction in pain intensity over 24 hours compared to placebo.

### 14.2 Adult Fever

The efficacy of OFIRMEV 1000 mg in the treatment of adult fever was evaluated in one randomized, double-blind, placebo-controlled clinical trial. The study was a 6-hour, single-dose, endotoxin-induced fever study in 60 healthy adult males. A statistically significant antipyretic effect of OFIRMEV was demonstrated through 6 hours in comparison to placebo. The mean temperature over time is shown in Figure 1.

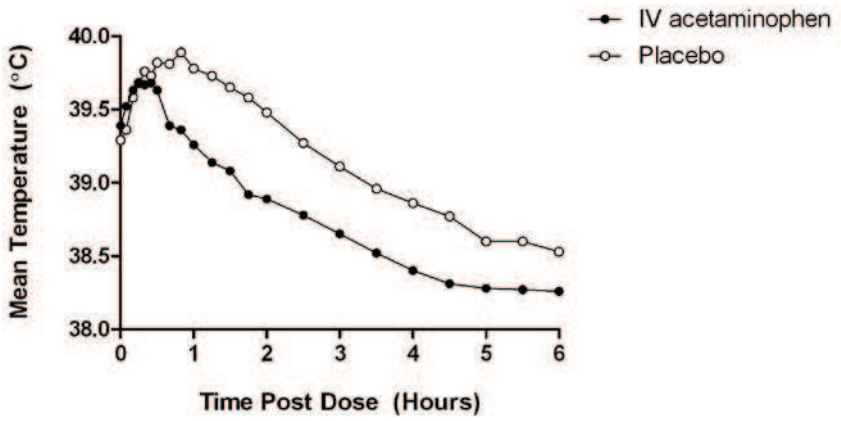



**Figure 1: Mean Temperature (°C) Over Time**

### 14.3 Pediatric Acute Pain and Fever

OFIRMEV was studied in 355 pediatric patients in two active-controlled and three open-label safety and pharmacokinetic trials [*see PEDIATRIC USE (8.4)*].

## 16 HOW SUPPLIED/STORAGE AND HANDLING

OFIRMEV is supplied in a 100 mL glass vial containing 1000 mg acetaminophen (10 mg/mL).
Carton of 24 vials, NDC 43825-102-01
OFIRMEV should be stored at 20 °C to 25 °C (68 °F to 77 °F) [See USP Controlled Room Temperature].
For single use only. The product should be used within 6 hours after opening. Do not refrigerate or freeze.

OFIRMEV (acetaminophen) Injection

Manufactured for:
Cadence Pharmaceuticals, Inc.
San Diego, CA 92130

Revised: 10/2013

 Label part number