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**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

MALLINCKRODT PHARMACEUTICALS
IRELAND LIMITED,

Plaintiff,

v.

ZYDUS PHARMACEUTICALS (USA) INC.
and CADILA HEALTHCARE LIMITED,

Defendants.

Civil Action No. _____

**COMPLAINT FOR
PATENT INFRINGEMENT**

(Filed Electronically)

Plaintiff Mallinckrodt Pharmaceuticals Ireland Limited (“Mallinckrodt” or “Plaintiff”), for its Complaint against Defendants Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Limited (collectively, “Zydus” or “Defendants”), hereby alleges as follows:

THE PARTIES

1. Plaintiff Mallinckrodt Pharmaceuticals Ireland Limited is a company organized and existing under the laws of Ireland, having a registered address of College Business & Technology Park, Cruiserath Road, Blanchardstown, Dublin 15, D15 TX2V, Ireland. Mallinckrodt is a wholly-

owned subsidiary of Mallinckrodt plc. As set forth herein, Mallinckrodt is the assignee of U.S. Patent No. 9,399,012 (“the ’012 patent”), U.S. Patent No. 9,610,265 (“the ’265 patent”), U.S. Patent No. 9,987,238 (“the ’238 patent”), and U.S. Patent No. 10,383,834 (“the ’834 patent”) (collectively, the “Patents-in-Suit”).

2. Upon information and belief, Defendant Zydus Pharmaceuticals (USA) Inc. (“Zydus USA”) is an entity organized and existing under the laws of the State of New Jersey, having a principal place of business at 73 Route 31 North, Pennington, New Jersey 08534.

3. Upon information and belief, Defendant Cadila Healthcare Limited (“Cadila”) is an entity organized and existing under the laws of India, having a principal place of business at Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, S.G. Highway, Ahmedabad, Gujarat, 382481, India.

4. Upon information and belief, Zydus USA is a wholly-owned subsidiary of Cadila.

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; 21 U.S.C. §§ 301 et seq.; 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. Upon information and belief, Cadila develops and manufactures generic versions of branded pharmaceutical products.

8. Upon information and belief, Cadila, either directly or through one or more of its agents, markets, distributes, sells, and/or imports generic versions of branded pharmaceutical products throughout the United States, including in this Judicial District.

9. Upon information and belief, Zydus USA markets, distributes, sells, and/or imports generic versions of branded pharmaceutical products developed and/or manufactured by Cadila throughout the United States, including in this Judicial District.

10. Zydus USA is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business in the State of New Jersey under Entity Identification No. 0100915422.

11. Zydus USA is registered with the State of New Jersey's Department of Health as a drug wholesaler under Registration No. 5003171.

12. Upon information and belief, Zydus USA, as an agent for Cadila, sent Mallinckrodt Hospital Products IP Limited ("Mallinckrodt Hospital Products IP," currently registered under the name "Mallinckrodt Hospital Products IP Unlimited Company") and Mallinckrodt Inc. a letter dated February 7, 2022 ("Zydus's Notice Letter"), stating that Zydus USA has submitted Abbreviated New Drug Application ("ANDA") No. 216467 ("Zydus's ANDA") seeking approval from the United States Food and Drug Administration ("FDA") to engage in the commercial manufacture, use, or sale within the United States (including, upon information and belief, in the State of New Jersey) of a generic version of OFIRMEV[®] (acetaminophen injection, 1,000 mg/100 mL (10 mg/mL) single-dose vials) ("Zydus's ANDA Product").

13. Upon information and belief, Zydus USA and Cadila are agents of each other with respect to importing generic versions of branded pharmaceutical products into the United States and commercially manufacturing, marketing, distributing, and/or selling generic versions of

branded pharmaceutical products throughout the United States, and will do the same with respect to Zydus's ANDA Product that is the subject of ANDA No. 216467, for which Zydus has sought approval from the FDA.

14. Upon information and belief, Zydus USA and Cadila are acting in concert with each other with respect to importing generic versions of branded pharmaceutical products into the United States and commercially manufacturing, marketing, distributing, and/or selling generic versions of branded pharmaceutical products throughout the United States, and will do the same with respect to Zydus's ANDA Product that is the subject of ANDA No. 216467, for which Zydus has sought approval from the FDA.

15. Upon information and belief, Zydus USA, as an agent for Cadila, submitted Zydus's ANDA with the FDA.

16. Upon information and belief, the actions of Zydus, such as, causing Zydus's ANDA to be submitted with the FDA and maintaining distribution channels throughout the United States, including in the State of New Jersey, establish that, if granted approval, Zydus will commercially manufacture, use, offer to sell, sell, and/or import Zydus's ANDA Product throughout the United States, including in New Jersey.

17. This Court has personal jurisdiction over Zydus USA, because, *inter alia*, Zydus USA: (1) is an entity organized and existing under the laws of the State of New Jersey; (2) has a principal place of business in New Jersey; (3) has purposely availed itself of the privilege of doing business in New Jersey, including, *inter alia*, by registering with the State of New Jersey's Division of Revenue and Enterprise Services to do business in the State of New Jersey under Business Identification No. 0100915422 and securing a New Jersey wholesale drug distributor's license under Registration No. 5003171; (4) markets, distributes, and sells generic versions of

branded pharmaceutical products throughout the United States, including in the State of New Jersey; (5) upon information and belief, derives substantial revenue from the sale of its products in the State of New Jersey; and (6) upon information and belief, intends to, directly or indirectly through its affiliate, agent, and/or alter ego, market, sell, or distribute Zydus's ANDA Product throughout the United States, including in the State of New Jersey.

18. This Court also has personal jurisdiction over Zydus USA because, *inter alia*, Zydus USA has availed itself of the legal protections of the State of New Jersey by previously consenting to personal jurisdiction and asserting counterclaims in this Judicial District. *See, e.g., Valeant Pharm. North Am. LLC, et al. v. Zydus Pharm. (USA) Inc. and Cadila Healthcare Ltd., et al.*, No. 2:18-13635 (BRM) (LDW) (D.I. 20, Defendants Zydus Pharmaceuticals (USA) Inc., Zydus Worldwide DMCC, and Cadila Healthcare Limited's Answer, Affirmative Defenses, and Counterclaims to Plaintiffs' Complaint for Patent Infringement, Mar. 5, 2019); *Takeda Pharm. Co. Ltd., et al. v. Zydus Pharm. (USA) Inc. and Cadila Healthcare Ltd.*, No. 3:18-11792 (FLW) (TJB) (D.I. 52, Answer, Affirmative Defenses, Counterclaims of Defendants, Apr. 29, 2019); *Janssen Prod., L.P., et al. v. Zydus Pharm. (USA) Inc. and Cadila Healthcare Ltd.*, No. 3:20-00787 (FLW) (TJB) (D.I. 13, Consent Judgment and Order, June 19, 2020); *Actelion Pharm. Ltd., et al. v. Zydus Pharm. (USA) Inc. and Cadila Healthcare Ltd.*, No. 3:19-22193 (BRM) (DEA) (D.I. 21, Consent Judgment and Order, July 10, 2020).

19. This Court has personal jurisdiction over Cadila, because, *inter alia*, Cadila: (1) has purposely availed itself of the privilege of doing business in New Jersey directly or indirectly through its subsidiary, agent, and/or alter ego; (2) maintains pervasive, continuous, and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic versions of branded pharmaceutical products in the State of New Jersey; (3) upon information and

belief, derives substantial revenue from the sale of its products in the State of New Jersey; and (4) upon information and belief, intends to, directly or indirectly through its subsidiary, agent, and/or alter ego, market, sell, or distribute Zydus's ANDA Product throughout the United States, including in the State of New Jersey.

20. This Court also has personal jurisdiction over Cadila because, *inter alia*, it has availed itself of the legal protections of the State of New Jersey by previously consenting to personal jurisdiction and asserting counterclaims in this Judicial District. *See, e.g., Valeant Pharm. North Am. LLC, et al. v. Zydus Pharm. (USA) Inc. and Cadila Healthcare Ltd., et al.*, No. 2:18-13635 (BRM) (LDW) (D.I. 20, Defendants Zydus Pharmaceuticals (USA) Inc., Zydus Worldwide DMCC, and Cadila Healthcare Limited's Answer, Affirmative Defenses, and Counterclaims to Plaintiffs' Complaint for Patent Infringement, Mar. 5, 2019); *Takeda Pharm. Co. Ltd., et al. v. Zydus Pharm. (USA) Inc. and Cadila Healthcare Ltd.*, No. 3:18-11792 (FLW) (TJB) (D.I. 52, Answer, Affirmative Defenses, Counterclaims of Defendants, Apr. 29, 2019); *Janssen Prod., L.P., et al. v. Zydus Pharm. (USA) Inc. and Cadila Healthcare Ltd.*, No. 3:20-00787 (FLW) (TJB) (D.I. 13, Consent Judgment and Order, June 19, 2020); *Actelion Pharm. Ltd., et al. v. Zydus Pharm. (USA) Inc. and Cadila Healthcare Ltd.*, No. 3:19-22193 (BRM) (DEA) (D.I. 21, Consent Judgment and Order, July 10, 2020).

21. Alternatively, this Court may exercise jurisdiction over Cadila pursuant to Fed. R. Civ. P. 4(k)(2) because, *inter alia*, (1) Mallinckrodt's claims arise under federal law; (2) Cadila is a foreign defendant not subject to personal jurisdiction in any state's court of general jurisdiction; and (3) Cadila has sufficient contacts with the United States as a whole, including, but not limited to, through its wholly-owned subsidiary, agent, and/or alter ego, submitting ANDAs to the FDA,

and importing, offering to sell, and/or selling pharmaceutical products throughout the United States, such that this Court's exercise of jurisdiction over Cadila satisfies due process.

22. This Court also has personal jurisdiction over Zydus because, *inter alia*, Zydus USA and Cadila have each committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement, including acts in the State of New Jersey, that have led to foreseeable harm and injury to Mallinckrodt in the State of New Jersey.

23. Venue is proper in this Court as to Zydus USA under 28 U.S.C. §§ 1391(b), (c), and/or (d), and 1400(b) because Zydus USA is an entity organized and existing under the laws of the State of New Jersey, has a principal place of business in New Jersey, and has committed and will commit further acts of infringement in this Judicial District. Venue is proper for the additional reasons set forth above and for other reasons that will be presented to the Court if such venue is challenged.

24. Venue is proper in this Court as to Cadila under 28 U.S.C. §§ 1391(c)(3) and 1400(b) because Cadila is a foreign corporation and may be sued in any judicial district in the United States in which Cadila is subject to the court's personal jurisdiction. Venue is proper for the additional reasons set forth above and for other reasons that will be presented to the Court if such venue is challenged.

THE PATENTS-IN-SUIT

25. Mallinckrodt owns the '012 patent, which was duly and legally issued on July 26, 2016 and is titled "Reduced Dose Intravenous Acetaminophen." A copy of the '012 patent is attached as Exhibit A.

26. Mallinckrodt owns the '265 patent, which was duly and legally issued on April 4, 2017 and is titled "Reduced Dose Intravenous Acetaminophen." A copy of the '265 patent is attached as Exhibit B.

27. Mallinckrodt owns the '238 patent, which was duly and legally issued on June 5, 2018 and is titled "Reduced Dose Intravenous Acetaminophen." A copy of the '238 patent is attached as Exhibit C.

28. Mallinckrodt owns the '834 patent, which was duly and legally issued on August 20, 2019 and is titled "Reduced Dose Intravenous Acetaminophen." A copy of the '834 patent is attached as Exhibit D.

OFIRMEV®

29. Mallinckrodt is the holder of New Drug Application ("NDA") No. 022450, by which the FDA granted approval of the first intravenous formulation of acetaminophen available in the United States that is marketed under the trade name OFIRMEV®.

30. OFIRMEV® (acetaminophen) injection is indicated for the management of mild to moderate pain in adult and pediatric patients 2 years and older, management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older, and reduction of fever in adult and pediatric patients.

31. Pursuant to 21 U.S.C. § 355(b)(1), the Patents-in-Suit are listed in the FDA publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the "Orange Book") with respect to OFIRMEV®.

ACTS GIVING RISE TO THIS ACTION

32. Upon information and belief, Zydus USA submitted ANDA No. 216467 to the FDA under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)(2)), seeking approval to

engage in the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Zydus's ANDA Product before the expiration of the Patents-in-Suit.

33. Zydus's ANDA No. 216467 contains certifications under 21 U.S.C. § 355(j)(2)(B)(iv)(II) ("Paragraph IV certification") with respect to the Patents-in-Suit.

34. On or about February 7, 2022, Zydus USA sent Mallinckrodt Hospital Products IP and Mallinckrodt Inc. Zydus's Notice Letter, in which it represented that Zydus USA had submitted ANDA No. 216467 for Zydus's ANDA Product and that Zydus's ANDA identified OFIRMEV[®] (acetaminophen) injection, 1,000 mg/100 mL (10 mg/mL) single-dose vials as the Reference Listed Drug and included Paragraph IV certifications with respect to the Patents-in-Suit.

35. Mallinckrodt Hospital Products IP first received Zydus's Notice Letter on or about February 9, 2022.

36. Mallinckrodt commenced this action within 45 days of the date of receipt of Zydus's Notice Letter.

COUNT I – INFRINGEMENT OF THE PATENTS-IN-SUIT

37. Mallinckrodt re-alleges paragraphs 1-36 as if fully set forth herein.

38. By seeking approval of ANDA No. 216467 to engage in the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Zydus's ANDA Product before the expiration of the Patents-in-Suit, Zydus has infringed the Patents-in-Suit under 35 U.S.C. § 271(e)(2)(A).

39. Mallinckrodt is entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of ANDA No. 216467 be a date that is not earlier than the latest expiration date of each of the Patents-in-Suit, including any patent term

extensions and/or patent term adjustments, the period of any pediatric exclusivity associated with the Patents-in-Suit, and additional periods of exclusivity to which Mallinckrodt is or becomes entitled.

40. The commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Zydus's ANDA Product, if approved by the FDA before the expiration of the Patents-in-Suit, for use in accordance with its proposed labeling, would infringe, induce, and/or contribute to the infringement of the Patents-in-Suit.

41. Mallinckrodt is entitled to a declaration that, if Zydus commercially manufactures, uses, offers to sell, or sells within the United States, and/or imports into the United States, Zydus's ANDA Product, or induces or contributes to any such conduct, it would further infringe the Patents-in-Suit pursuant to 35 U.S.C. §§ 271(a), (b), and/or (c).

42. Upon information and belief, Zydus was aware of the existence of the Patents-in-Suit and was aware that the submission of ANDA No. 216467 to the FDA constituted an act of infringement of the Patents-in-Suit.

43. Upon information and belief, Zydus was aware that the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Zydus's ANDA Product before the expiration of the Patents-in-Suit would constitute an act of infringement of the Patents-in-Suit.

44. Separate and apart from certain contentions regarding validity of the '012 patent, Zydus's Notice Letter does not identify any factual basis for, or any opinion of, noninfringement of Claims 1-15, 20, 22, 25-27, 29-31, 33, 34, 36-42, 45-50, 53, 54, 57, 58, 62-66, 69-71, 74-81, 84, 85, 88, 89, 93-97, 100-102, and 105-109 of the '012 patent.

45. Separate and apart from certain contentions regarding validity of the '265 patent, Zydus's Notice Letter does not identify any factual basis for, or any opinion of, noninfringement of Claims 1-4 and 6-10 of the '265 patent.

46. Separate and apart from certain contentions regarding validity of the '238 patent, Zydus's Notice Letter does not identify any factual basis for, or any opinion of, noninfringement of Claims 1-16 and 19-20 of the '238 patent.

47. Separate and apart from certain contentions regarding validity of the '834 patent, Zydus's Notice Letter does not identify any factual basis for, or any opinion of, noninfringement of Claims 1-6 and 8-11 of the '834 patent.

48. Mallinckrodt will be irreparably harmed by Zydus's infringing activities unless those activities are enjoined by this Court. Mallinckrodt does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Mallinckrodt respectfully requests the following relief:

A. A judgment that Zydus has infringed the Patents-in-Suit by submitting ANDA No. 216467 to the FDA;

B. A declaration that the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Zydus's ANDA Product will infringe or induce or contribute to the infringement of the Patents-in-Suit;

C. An order issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of ANDA No. 216467 be a date that is not earlier than the latest expiration date of the Patents-in-Suit, including any patent term extensions and/or patent term adjustments, the period of any pediatric exclusivity associated with the Patents-in-Suit, and additional periods of exclusivity to which Mallinckrodt is or becomes entitled;

D. A preliminary and permanent injunction restraining and enjoining Zydus, its directors, officers, agents, attorneys, affiliates, divisions, successors, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of any drug product, or use thereof, claimed in the Patents-in-Suit, before the latest expiration date of the Patents-in-Suit, including any patent term extensions and/or patent term adjustments, the period of any pediatric exclusivity associated with the Patents-in-Suit, and additional periods of exclusivity to which Mallinckrodt is or becomes entitled;

E. An award to Mallinckrodt of monetary relief if Zydus commercially manufactures, uses, offers for sale, or sells within the United States, and/or imports into the United States, Zydus's ANDA Product, or any other product that infringes or induces or contributes to the infringement of the Patents-in-Suit, before the latest expiration date of the Patents-in-Suit, including any patent term extensions and/or patent term adjustments, the period of any pediatric exclusivity associated with the Patents-in-Suit, and additional periods of exclusivity to which Mallinckrodt is or becomes entitled;

F. A declaration that this is an exceptional case and an award to Mallinckrodt of its reasonable expenses including attorneys' fees pursuant to 35 U.S.C. § 285;

G. An award to Mallinckrodt of costs in this action; and

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

Dated: March 21, 2022

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: March 21, 2022

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EXHIBIT A



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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(Continued)

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

US 9,399,012 B2

Page 2

(56)

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US 9,399,012 B2

1

**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, thiolicacetic 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.

2

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.

US 9,399,012 B2

3

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

4

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.

5 Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH 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

US 9,399,012 B2

5

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.

6

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%

US 9,399,012 B2

9

(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

10

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.

US 9,399,012 B2

11

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 simulta-

12

neously, 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-alphaacetylmethadol, levomethorphan, meptazinol, methadone, morphine, nalbuphine, nicomorphine, ohmefentanyl, opium, oripavine, oxycodone, oxymorphone, methadone, PEPAP, pentazocine, pethidine,

US 9,399,012 B2

13

phenazocine, piritamide, prodine, propoxyphene napsylate, remifentanyl, sufentanyl, 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 amoxicillin, benorilate, choline magnesium salicylate, diflusal, 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, sulfapyrazone, 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, dihydromorphone, noscapine, papverine, papaveretum, 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-HT₃ 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

14

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	Reduced	Reduced	Reduced	Reduced
	Glutathione	Glutathione	Glutathione	Glutathione	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

US 9,399,012 B2

15

16

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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

15

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

40

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 Hydrochloride Monohydrate	Cysteine Hydrochloride Monohydrate	Cysteine Hydrochloride Monohydrate	Cysteine Hydrochloride Monohydrate	Cysteine Hydrochloride 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

US 9,399,012 B2

17

Example 1D

18

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

25

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

50

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

US 9,399,012 B2

19

20

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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 of 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).

15 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

20 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/in²; (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 25 30 35 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 50 55 60 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

US 9,399,012 B2

21

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 $\geq 38^{\circ}$ 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

22

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.

US 9,399,012 B2

23

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

24

(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, acetylcysteine, 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.

US 9,399,012 B2

25

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

26

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.

US 9,399,012 B2

27

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, acetylcysteine, 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.

28

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.

US 9,399,012 B2

29

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.

30

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 B



US009610265B2

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

(10) **Patent No.:** **US 9,610,265 B2**
(45) **Date of Patent:** ***Apr. 4, 2017**

(54) **REDUCED DOSE INTRAVENOUS ACETAMINOPHEN**
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JP	1999-514013	11/1999
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OTHER PUBLICATIONS

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See application file for complete search history.

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(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.

20 Claims, No Drawings

US 9,610,265 B2

Page 2

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US 9,610,265 B2

1

**REDUCED DOSE INTRAVENOUS
ACETAMINOPHEN****CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 12/270,796, filed on Nov. 13, 2008, which 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 are incorporated herein by reference in their entirety to the full extent permitted by law.

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

2

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 pyralazone, 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,

US 9,610,265 B2

3

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.

4

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 4TH 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

5

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

6

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

US 9,610,265 B2

7

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%

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

8

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,

US 9,610,265 B2

11

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

12

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

US 9,610,265 B2

13

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-alphaacetyl-methadol, levomethorphan, meptazinol, methadone, morphine, nalbuphine, nicomorphine, ohmfentanyl, opium, oripavine, oxycodone, oxymorphone, methadone, PEPAP, pentazocine, pethidine, phenazocine, piritamide, prodine, propoxyphene napsylate, remifentanyl, sufentanyl, 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 amoxicillin, benorilate, choline magnesium salicylate, diflusal, 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, oxaprozol, 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, Pentazamine, Phenergan, Promacot, or Hydroxyzine); 5-HT₃ receptor antagonists (e.g., Dolasetron, Granisetron, Ondansetron, Tropisetron, or Palonosetron); and dopamine

14

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
<u>Excipients:</u>	
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.

US 9,610,265 B2

15

16

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
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

20

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

45

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 Hydrochloride	Cysteine Hydrochloride	Cysteine Hydrochloride	Cysteine Hydrochloride	Cysteine Hydrochloride
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

US 9,610,265 B2

17

Example 1D

IV Acetaminophen Formulations

Example 1D is prepared according to the procedure 5 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

25

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

50

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

18

US 9,610,265 B2

19

20

-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 of 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

15 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/in²; (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

US 9,610,265 B2

21

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 $\geq 38^{\circ}$ 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.

22

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 (n, 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 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 (n, 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.

US 9,610,265 B2

23

Descriptive statistics (n, 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 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)

24

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 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 of treating pain in a human subject weighing at least 50 kg comprising:
 - co-administering to the subject a therapeutically effective amount of a first pharmaceutical composition comprising about 500 mg to about 750 mg of acetaminophen and a therapeutically effective amount a second pharmaceutical composition comprising an opioid analgesic;
 - wherein the first pharmaceutical composition is administered to the subject intravenously.
2. The method of claim 1 wherein the administration of the first pharmaceutical composition to the subject is repeated at least once every four hours for a twenty-four hour period.

US 9,610,265 B2

25

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

4. The method of claim 3, wherein the first pharmaceutical composition is administered to the subject at least six times in a period of 24 hours.

5. The method of claim 3, wherein the first pharmaceutical composition is administered to the subject at least seven times in a period of 24 hours.

6. The method of claim 1, wherein the first pharmaceutical composition comprises about 600 mg to about 700 mg of acetaminophen.

7. The method of claim 1, wherein the first pharmaceutical composition comprises about 650 mg of acetaminophen.

8. The method of claim 1, wherein the opioid analgesic is selected from the group consisting of allylprodine, alphamethylfentanyl, alfentanil, bezitramide, buprenorphine, butorphanol, carfentanyl, codeine, dextropropoxyphene, dextromoramide, dezocine, diacetylmorphine, dihydrocodeine, dipapanone, dismorphine, dihydrocodeine, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, lefetamine, levorphanol, levo-alphaacetylmethadol, levomethorphan, meptazinol, methadone, morphine, nalbuphine, nicomorphine, ohmefentanyl, opium, oripavine, oxycodone, oxymorphone, methadone, phenethylphenylacetoxypiperidine (PEPAP), pentazocine, pethidine, phenazocine, piritamide, prodine, propoxyphene napsylate, remifentanyl, sufentanil, tilidine, thebaine, tramadol, and tapentadol.

9. The method of claim 8, wherein the opioid analgesic is selected from the group consisting of codeine, dihydrocodeine, hydrocodone, morphine, oxycodone, pentazocine, and tramadol.

10. The method of claim 8, wherein the opioid analgesic is morphine.

26

11. The method of claim 1, wherein the second pharmaceutical composition is administered to the subject orally, intravenously, rectally, or parenterally.

12. The method of claim 1, wherein the second pharmaceutical composition is administered as a single dose or in multiple doses.

13. The method of claim 1, wherein the first and second pharmaceutical compositions are administered simultaneously.

14. The method of claim 13, wherein the first and second pharmaceutical compositions are administered as a combined intravenous dosage form.

15. The method of claim 1, wherein the first and second pharmaceutical compositions are administered sequentially.

16. The method of claim 15, wherein the first pharmaceutical composition is administered prior to the second pharmaceutical composition or wherein the second pharmaceutical composition is administered prior to the first pharmaceutical composition.

17. The method of claim 15, wherein the timing between the administration of the first and second pharmaceutical compositions is from about 1 minute to less than about 12 hours.

18. The method of claim 15, wherein the timing between the administration of the first and second pharmaceutical compositions is from about 1 minute to less than about 6 hours.

19. The method of claim 15, wherein the timing between the administration of the first and second pharmaceutical compositions is from about 1 minute to less than about 3 hours.

20. The method of claim 15, wherein the timing between the administration of the first and second pharmaceutical compositions is from about 1 minute to less than about 1 hour.

* * * * *

EXHIBIT C



US009987238B2

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

(10) **Patent No.:** **US 9,987,238 B2**
(45) **Date of Patent:** ***Jun. 5, 2018**

(54) **REDUCED DOSE INTRAVENOUS ACETAMINOPHEN**
(71) Applicant: **MALLINCKRODT IP**, Dublin (IE)

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

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This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/436,285**

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(22) Filed: **Feb. 17, 2017**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 15/184,056, filed on Jun. 16, 2016, now Pat. No. 9,610,265, which is a continuation of application No. 12/270,796, filed on Nov. 13, 2008, now Pat. No. 9,399,012.

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(51) **Int. Cl.**
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A61K 9/00 (2006.01)
A61K 47/02 (2006.01)
A61K 47/26 (2006.01)

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(52) **U.S. Cl.**
CPC **A61K 31/167** (2013.01); **A61K 9/0019** (2013.01); **A61K 47/02** (2013.01); **A61K 47/26** (2013.01)

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(58) **Field of Classification Search**
USPC 514/629
See application file for complete search history.

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(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.

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US 9,987,238 B2

Page 3

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US 9,987,238 B2

1

**REDUCED DOSE INTRAVENOUS
ACETAMINOPHEN****CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 15/184,056, filed on Jun. 16, 2016, which is a continuation of U.S. patent application Ser. No. 12/270,796, filed on Nov. 13, 2008, which 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 are incorporated herein by reference in their entirety to the full extent permitted by law.

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

2

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 pyralazone, 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,

US 9,987,238 B2

3

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.

4

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 4TH 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

5

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

6

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

US 9,987,238 B2

7

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%

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

8

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

US 9,987,238 B2

9

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

10

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,

US 9,987,238 B2

11

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

12

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

US 9,987,238 B2

13

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-alphaacetyl-methadol, levomethorphan, meptazinol, methadone, morphine, nalbuphine, nicomorphine, ohmfentanyl, opium, oripavine, oxycodone, oxymorphone, methadone, PEPAP, pentazocine, pethidine, phenazocine, piritamide, prodine, propoxyphene napsylate, remifentanyl, sufentanyl, 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, diflusal, 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, Pentazamine, Phenergan, Promacot, or Hydroxyzine); 5-HT₃ receptor antagonists (e.g., Dolasetron, Granisetron, Ondansetron, Tropisetron, or Palonosetron); and dopamine

14

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
<u>Excipients:</u>	
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.

US 9,987,238 B2

15

16

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
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

20

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

45

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 Hydrochloride	Cysteine Hydrochloride	Cysteine Hydrochloride	Cysteine Hydrochloride	Cysteine Hydrochloride
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

US 9,987,238 B2

17

Example 1D

18

IV Acetaminophen Formulations

Example 1D is prepared according to the procedure 5 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

25

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

50

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

US 9,987,238 B2

19

20

-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.

15 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

20 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/in²; (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

US 9,987,238 B2

21

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 $\geq 38^{\circ}$ 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

22

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

US 9,987,238 B2

23

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 sat-

24

isfaction 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 1g 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 of treating pain in a human subject, in need thereof, weighing at least 50 kg comprising:

administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising about 500 mg to about 750 mg of acetaminophen; and repeating the administration at least once every four hours;

wherein the pharmaceutical composition is administered to the subject intravenously; and

wherein the therapeutic effect of the pharmaceutical composition is comparable to the standard of care treatment of 1000 mg of acetaminophen administered orally every 6 hours.

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

3. The method of claim 1, wherein the pharmaceutical composition is administered to the subject at least six times in a period of 24 hours.

US 9,987,238 B2

25

4. The method of claim 1, wherein the pharmaceutical composition comprises about 600 mg to about 700 mg of acetaminophen.

5. The method of claim 1, wherein the pharmaceutical composition comprises about 650 mg of acetaminophen.

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

7. The method of claim 6, wherein the antioxidant is cysteine hydrochloride monohydrate.

8. The method of claim 1, wherein the pharmaceutical composition further comprises a buffering agent.

9. The method of claim 5, wherein the buffering agent is selected from the group consisting of a pharmaceutically acceptable salt or acid of citrate, phosphate, acetate, glutamate, tartate, benzoate, lactate, histidine or other amino acids, gluconate, malate, succinate, formate, propionate, carbonate, and any combinations thereof.

10. The method of claim 5, wherein the buffering agent is disodium phosphate dehydrate.

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

12. The method of claim 1, wherein the pharmaceutical composition has a pH between about 5 to about 6.

26

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

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

15. The method of claim 14, wherein the isotonicity agent is selected from the group consisting of: dextrose, mannitol, and lactose.

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

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

18. The method of claim 17, wherein the lyophilized powder is reconstituted in solution prior to administration.

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

20. The method of claim 1, wherein the pharmaceutical composition is intravenously administered to the subject over about 15 minutes.

* * * * *

EXHIBIT D



US010383834B2

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

(10) **Patent No.:** **US 10,383,834 B2**
(45) **Date of Patent:** ***Aug. 20, 2019**

(54) **REDUCED DOSE INTRAVENOUS ACETAMINOPHEN**

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

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 15/436,285, filed on Feb. 17, 2017, now Pat. No. 9,987,238, which is a continuation of application No. 15/184,056, filed on Jun. 16, 2016, now Pat. No. 9,610,265, which is a continuation of application No. 12/270,796, filed on Nov. 13, 2008, now Pat. No. 9,399,012.

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

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 CPC A61K 31/16
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(56) **References Cited**
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(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.

12 Claims, No Drawings

US 10,383,834 B2

1

**REDUCED DOSE INTRAVENOUS
ACETAMINOPHEN****CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 15/436,285, filed on Feb. 17, 2017, which is a continuation of U.S. patent application Ser. No. 15/184,056, filed on Jun. 16, 2016, which is a continuation of U.S. patent application Ser. No. 12/270,796, filed on Nov. 13, 2008, which 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 are incorporated herein by reference in their entirety to the full extent permitted by law.

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.

2

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 pyralazone, 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 composition 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.

US 10,383,834 B2

3

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

4

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 4TH 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

US 10,383,834 B2

5

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.

6

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).

US 10,383,834 B2

7

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

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

8

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

US 10,383,834 B2

9

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

10

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,

US 10,383,834 B2

11

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

12

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 admin-

US 10,383,834 B2

13

istered 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, dipipanone, dismorphine, dihydrocodeine, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, lefetamine, levorphanol, levo-alphaacetyl-methadol, levomethorphan, meptazinol, methadone, morphine, nalbuphine, nicomorphine, ohmefentanyl, opium, oripavine, oxycodone, oxymorphone, methadone, PEPAP, pentazocine, pethidine, phenazocine, piritamide, prodine, propoxyphene napsylate, remifentanyl, sufentanyl, 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 amoxicillin, benorilate, choline magnesium salicylate, diflusal, 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, papaverine, papaveretum, 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

14

not limited to, antihistamines (e.g., Cyclizine, Diphenhydramine, Dimenhydrinate, Meclizine, Promethazine, Pentazine, Phenergan, Promacot, or Hydroxyzine); 5-HT₃ 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.

US 10,383,834 B2

15

16

Formula 1(A)					
Acetaminophen	0.550 g	0.650 g	0.750 g	0.850 g	0.950 g
<u>Excipients:</u>					
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
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 ²⁰ outlined in Example 2 using the amounts of the excipients described in Example 1.

Formula 1(B)					
Acetaminophen	0.550 g	0.650 g	0.750 g	0.850 g	0.950 g
<u>Excipients:</u>					
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 ⁴⁰ outlined in Example 2 using the amounts of the excipients described in Example 1.

Formula 1(C)					
Acetaminophen	0.550 g	0.650 g	0.750 g	0.850 g	0.950 g
<u>Excipients:</u>					
Antioxidant	Cysteine Hydrochloride Monohydrate	Cysteine Hydrochloride Monohydrate	Cysteine Hydrochloride Monohydrate	Cysteine Hydrochloride Monohydrate	Cysteine Hydrochloride 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 ⁶⁵ outlined in Example 2 using the amounts of the excipients described in Example 1.

US 10,383,834 B2

17

18

Formula 1(D)					
Acetaminophen	0.550 g	0.650 g	0.750 g	0.850 g	0.950 g
Excipients:					
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	0.550 g	0.650 g	0.750 g	0.850 g	0.950 g
Excipients:					
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	0.550 g	0.650 g	0.750 g	0.850 g	0.950 g
Excipients:					
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
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

60

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.

65

US 10,383,834 B2

19

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/in²; (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);

20

(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.

US 10,383,834 B2

21

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 $\geq 38^{\circ}$ 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 (n, 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.

22

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 (n, 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 (n, 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

US 10,383,834 B2

23

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

24

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 of treating pain in a human subject weighing at least 50 kg comprising:

administering to the subject an intravenous acetaminophen formulation comprising about 650 mg of acetaminophen; and

repeating the administration of the intravenous acetaminophen formulation every four hours;

wherein the subject receives a maximum daily dose of less than 4000 mg of acetaminophen per day.

2. The method of claim 1, wherein intravenous acetaminophen formulation is a sterile solution.

3. The method of claim 1, wherein the intravenous acetaminophen formulation is administered to the subject over about 5 minutes to about 30 minutes.

4. The method of claim 1, wherein the intravenous acetaminophen formulation is administered to the subject over about 15 minutes.

5. The method of claim 1, wherein the subject is suffering from acute pain.

6. The method of claim 1, wherein the subject is suffering from postoperative pain.

7. The method of claim 1, wherein the intravenous acetaminophen formulation is a lyophilized powder that is reconstituted prior to administration to the subject.

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

administering to the subject an intravenous acetaminophen formulation comprising about 650 mg of acetaminophen; and

repeating the administration of the intravenous acetaminophen formulation every four hours;

wherein the subject receives a maximum daily dose of less than 4000 mg of acetaminophen per day.

9. The method of claim 8, wherein intravenous acetaminophen formulation is a sterile solution.

10. The method of claim 8, wherein the intravenous acetaminophen formulation is administered to the subject over about 5 minutes to about 30 minutes.

11. The method of claim 8, wherein the intravenous acetaminophen formulation is administered to the subject over about 15 minutes.

12. The method of claim 8, wherein the intravenous acetaminophen formulation is a lyophilized powder that is reconstituted prior to administration to the subject.

* * * * *