PHARMACEUTICAL FORMULATIONS CONTAINING METHYLNALTREXONE

FIELD OF THE INVENTION

This invention relates to methylnaltrexone pharmaceutical preparations, methylnaltrexone formulations, methylnaltrexone kits, and methods of making the same.

BACKGROUND OF THE INVENTION

Quaternary amine opioid antagonist derivatives have been shown to have utility in a number of contexts. They are considered peripherally acting only, and, therefore, find particular utility in reducing the side-effects of opioids without reducing the analgesic effect of opioids. Such side effects include nausea, emesis, dysphoria, pruritis, urinary retention, bowel hypomotility, constipation, gastric hypomotility, delayed gastric emptying and immune suppression. The utility of these peripherally acting opioid antagonists is not limited to reducing side-effects stemming from opioid analgesic treatment. Instead, these derivatives also have utility in circumstances where endogenous opioids alone (or in conjunction with exogenous opioid treatment) cause undesirable conditions such as ileus and other such conditions including, but not limited to, those mentioned above.

Methylnaltrexone is a quaternary amine opioid antagonist derivative, discovered in the mid-70s. Methylnaltrexone and some of its uses are described in U.S. Patents 4,176,186, 4,719,215, 4,861,781, 5,102,887, 5,972,954, and 6,274,591. Stable formulations of methylnaltrexone, however, have heretofore not existed. Methylnaltrexone apparently was assumed to have a structure that was inherently stable. The stability of a pharmaceutical composition in solution, however, is not necessarily predictable either over time when stored at room temperature or when autoclaved.

Naloxone is an opioid antagonist that acts both centrally and peripherally. It differs structurally from methylnaltrexone and would be expected to have a different stability in solution. An allegedly stable formulation of naloxone is described in U.S. Patent No. 5,866,154.

Surprisingly, it has been discovered that methylnaltrexone is unusually unstable. It further has been discovered that methylnaltrexone has certain degradation products different from those of naloxone. It also has been discovered that critical parameters and conditions are required for stable formulations of methylnaltrexone.

SUMMARY OF THE INVENTION

In one aspect, the invention provides a composition or preparation that is a solution of methylnaltrexone or a salt thereof, wherein the preparation after autoclaving has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation. Preferably, the concentration of such degradation products does not exceed 1.5%, 1%, 0.5%, 0.25%, or even 0.125% of the methylnaltrexone or salt thereof in the preparation. The composition or preparation can contain one of, any combination of, or all of a chelating agent, a buffering agent, an anti-oxidant, a cryoprotecting agent, an isotonicity agent and an opioid. The preferred chelating agent is disodium edetate or a derivative thereof. The disodium edetate preferably is at a concentration ranging from between 0.001 and 100 mg/ml, more preferably 0.05 to 25.0 mg/ml, and even more preferably, 0.1 to 2.5 mg/ml. A preferred buffering agent is citrate buffer. The citrate buffer typically is in a concentration ranging from 0.001 to 100.0 mM, preferably from 0.1 to 10 mM, and more preferably, 0.1 to 5.0 mM. A preferred cryoprotecting agent is mannitol.

The composition or preparation preferably has a pH that does not exceed 4.25. More preferably, the pH ranges from 2.0 to 4.0, 3.0 to 4.0, and most preferably, from 3.0 to 3.5.

Accordingly, the present invention provides a stable pharmaceutical preparation comprising methylnaltrexone or a salt thereof, wherein:

(a) the preparation is an aqueous formulation and the concentration of methylnaltrexone degradation products in the preparation does not exceed 2% of the methylnaltrexone or salt thereof after

i) autoclaving, or

ii) storage at about room temperature,

(b) the preparation is an aqueous formulation and the preparation has a pH below 4.25,

(c) the preparation is an aqueous formulation and the preparation further comprises a chelating agent in an amount such that the preparation after autoclaving has a concentration of methylnaltrexone degradation products that does not exceed 0.5% of the methylnaltrexone or salt thereof in the preparation,

(d) the preparation is an aqueous formulation and the preparation further comprises at least one methylnaltrexone degradation inhibiting agent selected from the group

consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof, wherein the preparation has a pH ranging from 2 to 6, wherein the preparation is processed under at least one sterilization technique, and wherein the preparation has a concentration of methylnaltrexone degradation products that is less than 1.5%, 1.0%, 0.5%, 0.25% or 0.125%, and/or

(e) the preparation is a lyophilised formulation of methylnaltrexone, wherein the formulation upon reconstitution in water at a concentration of 20 mg/ml has a pH of between 2 and 6, or 3 and 5, and optionally includes a cryoprotecting agent in an amount sufficient to render the formulation stable.

According to another aspect of the invention, a composition or preparation is provided, which includes a solution of methylnaltrexone or a salt thereof, wherein the preparation after storage at about room temperature for six months has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone in the preparation. The concentration of the methylnaltrexone degradation products preferably does not exceed 1.5%, 1.0%, 0.5%, 0.25%, and even 0.125% of the methylnaltrexone in the preparation. The composition or preparation can contain one of, any combination of, or all of a chelating agent, a buffering agent, an anti-oxidant, a cryoprotecting agent, an isotonicity agent and an opioid. The preferred chelating agent and concentrations are as described above. The preferred buffering agent and concentrations are as described above. Preferably, the composition or preparation has a pH that does not exceed 4.25. The preferred pHs and ranges are as described above.

According to another aspect of the invention, a stable composition or preparation is provided. The composition or preparation is a solution of methylnaltrexone or a salt

thereof wherein the pH is below 4.25. Preferably, the pH is between 2.75 and 4.25, more preferably, between 3.0 and 4.0, and most preferably, between 3.0 and 3.5. According to conventional procedures, pH can be adjusted with an acid. Examples of acids useful for this purpose include hydrochloric acid, citric acid, sulfuric acid, acetic acid, and phosphoric acid. The stable composition or preparation can also include any one of, any combination of, or all of a chelating agent, a buffering agent, an isotonicity agent, an antioxidant, a cryogenic agent, and an opioid.

According to another aspect of the invention, a stable composition or preparation is provided. The composition or preparation is a solution of methylnaltrexone or salt thereof, wherein the solution further comprises a chelating agent in an amount sufficient to inhibit degradation of the methylnaltrexone or salt thereof, whereby the amount is such that the composition or preparation after autoclaving has a concentration of methylnaltrexone degradation products that does not exceed 0.5%, 0.25% or even 0.125% of the methylnaltrexone or salt thereof in the composition or preparation. The composition or preparation can further include any one of, any combination of, or all of a buffering agent, an isotonicity agent, an antioxidant and an opioid. Preferred chelating agents, buffering agents and pHs are as described above.

According to another aspect of the invention, a composition or preparation is provided. The composition or preparation is a solution of methylnaltrexone or salt thereof in at least one methylnaltrexone degradation inhibiting agent. The agent can be any one of, any combination of, or all of a chelating agent, a buffering agent, and an antioxidant, provided that the solution has a pH ranging from 2.0 to 6.0. The degradation inhibiting agent is present in an amount sufficient to render the composition or preparation stable, wherein the composition or preparation is processed under at least one sterilization technique, and wherein the composition or preparation is substantially free of methylnaltrexone degradation products. The composition or preparation can be stable to storage for at least six months, at least twelve months, or at least twenty-four months, at about room temperature. Preferably, the composition or preparation is stable after autoclaving. The composition or preparation further may include either or both of an isotonicity agent and an opioid. Preferably, the pH of the solution is between 2.75 and 4.25, more preferably, between 3.0 and 4.0, and most preferably, between 3.0 and 3.5.

In any one of the foregoing aspects of the invention, the composition or preparation can be a pharmaceutical composition.

In any one of the foregoing aspects of the invention, the methylnaltrexone can be present in a therapeutically effective amount. In some embodiments, the concentration of methylnaltrexone ranges from 0.01 to 100 mg/ml. In other embodiments, the methylnaltrexone concentration ranges between 0.1 and 100.0 mg/ml. In other embodiments, the methylnaltrexone ranges between 1.0 and 50.0 mg/ml.

In any one of the foregoing embodiments, the methylnaltrexone can be present in an amount sufficient to treat nausea, emesis, dysphoria, pruritus, urinary retention, ileus, post-operative ileus, post-partum ileus, paralytic ileus, bowel hypomotility, constipation, gastric hypomotility, delayed gastric emptying, decreased biliary secretion, decreased pancreatic secretion, biliary spasm, increased sphincter tone, cutaneous flushing, impaction, sweating, inhibition of gastrointestinal motility, inhibition of gastric emptying, gastrointestinal dysfunction, incomplete evacuation, bloating, abdominal distention, increased gastroesophageal reflux, hypotension, bradycardia, irritable bowel syndrome, or immunosuppression.

In any of the foregoing embodiments, the methylnaltrexone can be present in an amount sufficient to accelerate discharge from hospital post-surgery (including abdominal surgeries such as rectal resection, colectomy, stomach, esophageal, duodenal, appendectomy, hysterectomy, or non-abdominal surgeries such as orthopedic, trauma injuries, thoracic or transplantation), for example, by accelerating bowel sounds after surgery, or speeding the time to first food intake or first bowel movement. In other important embodiments, the amount is sufficient to induce laxation. This has particular application where the subject is a chronic opioid user.

In any one of the foregoing embodiments, the solution of methylnaltrexone or salt thereof may be contained in a sealed container such as a bottle, an infusion bag, a syringe, a vial, a vial with a septum, an ampoule, an ampoule with a septum, or a syringe. The container may include indicia indicating that the solution has been autoclaved or otherwise subjected to a sterilization technique.

According to another aspect of the invention, any of the foregoing embodiments is lyophilized, preferably in the presence of a cryoprotecting agent. The invention therefore provides a lyophilized preparation of methylnaltrexone. Preferably, the

lyophilized preparation is a stable preparation, containing less than 1%, less than 0.5%, less than 0.25% and even less than 0.125% methylnaltrexone degradation product. The preparation can contain a cryoprotecting agent, which preferably is neutral or acidic in water.

According to another aspect of the invention, a product is provided. The product is a stable lyophilized formulation of methylnaltrexone, wherein the formulation upon reconstitution and water at a concentration of 20 mg/ml has a pH of between 2 and 6. In some embodiments, the formulation upon reconstitution has a pH of about 2, about 3, about 4, about 5, or about 6. The formulation can include a cryoprotecting agent present in amounts sufficient to render the formulation stable. The cryoprotecting agent in important embodiments are polymerized carbohydrates. A preferred cryoprotecting agent is mannitol. Any one of the foregoing solutions described above can be lyophilized. It therefore is an aspect of the invention that such materials include one or any combination of a buffering agent, a chelating agent, an antioxidant, and an isotonicity agent. Preferred materials are as described above.

According to still another aspect of the invention, a product is provided that includes methylnaltrexone and the degradation inhibiting agent selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof, wherein the degradation inhibiting agent is present in an amount sufficient to render stable the solution of the product containing a concentration of 20 mg/ml methylnaltrexone in water. Preferably, the product when in solution at a concentration of 20 mg/ml methylnaltrexone yields a pH of between 2 and 6.

According to another aspect of the invention, a pharmaceutical preparation is provided. The pharmaceutical preparation contains methylnaltrexone, sodium chloride, citric acid, trisodium citrate, and disodium edetate. In one important embodiment, the methylnaltrexone is present between 20 and 40 mg/ml, the sodium chloride is present between 2 and 6 mg/ml, the citric acid is present between 0.05 and 0.1 mg/ml, the trisodium citrate is present between 0.025 and 0.075 mg/ml, and the disodium edetate is present between 0.5 and 1.0 mg/ml.

The buffering agent may be any pharmaceutically acceptable buffering agent. Common buffering agents include citric acid, sodium citrate, sodium acetate, acetic acid, sodium phosphate and phosphoric acid, sodium ascorbate, tartaric acid, maleic acid,

glycine, sodium lactate, lactic acid, ascorbic acid, imidazole, sodium bicarbonate and carbonic acid, sodium succinate and succinic acid, histidine, and sodium benzoate and benzoic acid. The preferred buffering agent is a citrate buffering agent.

The chelating agent may be any pharmaceutically acceptable chelating agent. Common chelating agents include ethylenediaminetetraacetic acid (EDTA) and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, and sodium desoxycholate and derivatives thereof. The preferred chelating agent is disodium edetate.

The antioxidant may be any pharmaceutically acceptable antioxidant. Common antioxidants include those selected from the group consisting of an ascorbic acid derivative, butylated hydroxy anisole, butylated hydroxy toluene, alkyl gallate, sodium meta-bisulfite, sodium bisulfite, sodium dithionite, sodium thioglycollic acid, sodium formaldehyde sulfoxylate, tocopherol and derivatives thereof, monothioglycerol, and sodium sulfite. The preferred antioxidant is monothioglycerol.

The cryoprotecting agent may be any pharmaceutically acceptable cryoprotecting agent. Common cryoprotecting agents include histidine, polyethylene qlycol, polyvinyl pyrrolidine, lactose, sucrose, and mannitol. Improtant cryoprotecting agents are polyols. The preferred cryoprotecting agent of the invention is mannitol.

The opioid can be any pharmaceutically acceptable opioid. Common opioids are those selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol.

The isotonicity agent can be any pharmaceutically acceptable isotonicity agent. Common isotonicity agents include those selected from the group consisting of sodium chloride, mannitol, lactose, dextrose, glycerol, and sorbitol. The preferred isotonicity agent is mannitol.

The pharmaceutical preparation may optionally comprise a preservative. Common preservatives include those selected from the group consisting of chlorobutanol, parabens, thimerosol, benzyl alcohol, and phenol.

According to another aspect of the invention, a method is provided for preparing an autoclaved preparation of a solution of methylnaltrexone or salts thereof, whereby the autoclaved preparation has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation. The method involves providing a solution, having a pH of 4.25 or less, of methylnaltrexone or a salt thereof, and being substantially free of methylnaltrexone degradation products, and autoclaving the solution. The solution can contain, optionally, any one of, any combination of, or all of a chelating agent, an isotonicity agent, a buffering agent, an antioxidant, a cryoprotecting agent, and an opioid. Preferably, the pH of the solution ranges from 2.0 to 4.0. More preferably, from 3.0 to 4.0, and most preferably from 3.0 to 3.5. Preferred chelating agents, isotonicity agents, buffering agents, antioxidants, cryoprotecting agents, and opioids are as described above. Preferred concentrations of methylnaltrexone, likewise, are as described above.

According to another aspect of the invention, a method is provided for preparing an autoclaved preparation. The preparation has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation. The method involves providing a solution containing methylnaltrexone or salt thereof and a chelating agent, the solution being substantially free of methylnaltrexone degradation products, and then autoclaving the solution. The chelating agent is present in an amount sufficient to protect the preparation against substantial unwanted degradation of methylnaltrexone or its salt, and maintain the solution to be substantially free of methylnaltrexone degradation products. Preferred chelating agents and concentrations thereof are as described above. The preparation may include, optionally, any one of, any combination of, or all of a buffering agent, an isotonicity agent, an antioxidant, a cryoprotecting agent, and an opioid. Preferred buffering agents, isotonicity agents, antioxidants and opioids, as well as concentrations, are as described above. Preferred pHs of the solution likewise are as described above. Preferably, the degradation products after autoclaving do not exceed 1.5%, 1%, 0.5%, 0.25%or even 0.125%.

According to another aspect of the invention, a method is provided for inhibiting the formation of methylnaltrexone degradation products in a preparation that is a solution of methylnaltrexone or salts thereof. The method involves preparing an aqueous solution containing at least one methylnaltrexone degradation inhibiting agent selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, a cryoprotecting agent, and combinations thereof. A powdered source of methylnaltrexone or salt thereof is dissolved into the solution to form the preparation. The preparation has or is adjusted without addition of a pH-adjusting base to have a pH of between 2 and 6. More preferably, the pharmaceutical preparation is adjusted to have a pH ranging from 3 to 5, more preferably, 3 to 4, and most preferably, 3.0 to 3.5. An isotonicity agent may be added to the solution. Likewise, an opioid may be added to the solution.

In any one of the foregoing aspects of the invention, the preparation can be a pharmaceutical preparation.

According to another aspect of the invention, a method is provided for preparing a stable pharmaceutical preparation that is an aqueous solution of methylnaltrexone or salts thereof to inhibit formation of methylnaltrexone degradation products. A solution is provided containing methylnaltrexone or salts thereof and at least one methylnaltrexone degradation inhibiting agent. The solution is processed under at least one sterilization technique prior to and/or after terminal filling the solution in a sealable container to form the stable pharmaceutical preparation, wherein the method is carried out without the addition of pH-adjusting base to the solution. The methylnaltrexone degradation inhibiting agent can be selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof. An isotonicity agent can be added. A cryoprotecting agent can also be added. Likewise, an opioid can be added. Preferred chelating agents, buffering agents, antioxidants, isotonicity agents, cryoprotecting agents, and opioids are as described above. Preferred concentrations are as described above. The solution may be processed to adjust the pH. This is preferably done using an acid. Most preferably, the solution is adjusted to a range between a pH of 2 and 6, more preferably, between 3 and 5, 3 and 4, and most preferably between 3.0 and 3.5. The material can be contained in a sealed container. The container can be purged with nitrogen and/or sparged to eliminate oxygen.

Accordingly, the present invention provides a method of producing a pharmaceutical preparation comprising methylnaltrexone or a salt thereof, which is stable to the formation of methylnaltrexone degradation products, the method comprising:

providing an aqueous formulation of methylnaltrexone or a salt thereof, the aqueous formulation being substantially free of methylnaltrexone degradation products and:

i) having a pH of 4.25 or less, and/or

ii) further comprising a chelating agent, buffering agent, and/or an antioxidant,

and optionally autoclaving the aqueous formulation.

In some embodiments of the invention, parenteral formulations are provided. In one embodiment, the formulation made by dissolving methylnaltrexone diluted in water, to which mannitol is added. The solution is then filter sterilized followed by lyophilization. Therefore, the product may be provided in lyophilized form, and in combination with certain cryoprotectants such as mannitol or lactose. Optionally, a reconstituting diluent is provided, such as a physiological saline diluent.

According to another aspect of the invention, a kit is provided. The kit is a package containing a sealed container comprising any one of the preparations described above, together with instructions for use. The kit can also include a diluent container containing a pharmaceutically acceptable diluent. The kit can further comprise instructions for mixing the preparation and the diluent. The diluent can be any pharmaceutically acceptable diluent. Well known diluents include 5% dextrose solution and physiological saline solution. The container can be an infusion bag, a sealed bottle, a vial, a vial with a septum, an ampoule, an ampoule with a septum, an infusion bag or a syringe. The kit further can contain an opioid container containing an opioid. The containers can optionally include indicia indicating that the containers have been autoclaved or otherwise subjected to sterilization techniques. The kit can include instructions for administering the various solutions contained in the containers to subjects.

The invention also involves methods of treatment. According to another aspect of the invention, a method is provided for treating a subject in need of such treatment with an effective amount of methylnaltrexone or a salt thereof. The method involves administering to the subject an effective amount of methylnaltrexone or salt thereof in any one of the pharmaceutical preparations described above, detailed herein, and/or set forth in the claims. In one aspect, the method is a method for inhibiting a peripheral opioid receptor in a human subject. In another aspect, the method is for reducing a side-effect of opioid treatment. In another aspect, the method is for treating any one of a condition selected from the group consisting of nausea, emesis, dysphoria, pruritus, urinary retention, ileus, post-operative ileus, post-partumileus, parallytic ileus, bowel hypomotility, constipation, gastric hypomotility, delayed gastric emptying, decreased biliary secretion, decreased pancreatic secretion, biliary spasm, increased sphincter tone, cutaneous flushing, impaction, sweating, inhibition of gastrointestinal motility, inhibition

of gastric emptying, gastrointestinal dysfunction, incomplete evacuation, bloating, abdominal distention, increased gastroesophageal reflux, hypotension, bradycardia, irritable bowel syndrome, or immunosuppression.

In any of the foregoing embodiments, the methylnaltrexone can be present in an amount sufficient to accelerate discharge from hospital post-surgery, accelerate bowel sounds after surgery, or induce laxation.

The subject can be any subject in need of such treatment. Important subjects include those receiving opioids including opioids for pain, cancer or surgical patients, or immunosuppressed or immunocompromised patients (including HIV infected patients), patients with advanced medical illness, terminally ill patients, patients with neuropathies, patients with rheumatoid arthritis, patients with osteoarthritis, patients with chronic pack pain, patients with spinal cord injury, patients with chronic abdominal pain, patients with chronic pancreatic pain, patients with pelvic/perineal pain, patients with fibromyalgia, patients with chronic fatigue syndrome, patients with migraine or tension headaches, patients on hemodialysis, and patients with sickle cell anemia.

The invention also provides the use of the pharmaceutical preparation of the invention for the manufacture of a medicament for treating a side effect associated with opioid treatment. In particular, the side effect may be constipation.

In the foregoing description, applicants have described the invention in connection with methylnaltrexone or salts thereof. Such salts include, but are not limited to, bromide salts, chloride salts, iodide salts, carbonate salts, and sulfate salts. It should be understood, however, that methylnaltrexone is a member of a class of compounds known as quaternary derivatives of noroxymorphone, as disclosed in U.S. Patent No. 4,176,186, the entire disclosure of which is incorporated herein by reference. It is believed that the invention extends to any such quaternary derivative of noroxymorphone, and the invention is intended to embrace pharmaceutical preparations, methods and kits containing such derivatives. Another aspect of the invention then embraces the foregoing summary but read in each aspect as if any such derivative is substituted wherever "methylnaltrexone" appears. Likewise, the invention also embraces each and every claim read as if the term "quaternary derivative of noroxymorphone" were substituted whenever "methylnaltrexone" appears.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph depicting methylnaltrexone degradation products eluting from a column at time zero (peak Nos. 1, 2 and 4 are degradation products; peak No 4 is methylnaltrexone; peak no 5. O-methylnaltrexone bromide).

Figure 2 is a graph depicting methylnaltrexone degradation products eluting from a column at 12 months (peak Nos. 1, 2 and 4 are degradation products; peak No 4 is methylnaltrexone; peak no 5. O-methylnaltrexone bromide).

Figure 3 is a schematic representation of a kit according to the invention containing the formulations described herein.

DETAILED DESCRIPTION OF THE INVENTION

Applicants have discovered that during the autoclaving process, methylnaltrexone in aqueous solution tends to degrade to a surprising extent. The amount of degradation resulting from simple autoclaving (122 °C, 15 lbs. pressure for 20 min.) can be as high as 10%. The degradation products are depicted in Figure 1, and appear to include at least two predominant degradants having relative retention times (RRT) of 0.72 (2.828 minutes) and 0.89 (3.435 minutes) and, with other minor forms as can be observed. The degradant identified by the 0.72 RRT peak appears in small amounts, 0.074, immediately upon dissolving the methylnaltrexone into solution and increases overtime with storage or autoclaving 0.25%. The degradant identified by the 0.89 RRT peak appears only after storage over time or after autoclaving (<0.05% and 0.724%, respectively). Applicants also have discovered that methylnaltrexone is unstable in aqueous solutions when stored at room temperature or even at 4 °C for significant (but commercially necessary) periods of time such as 6 months, 12 months or even two years. Degradation occurs without regard to whether the aqueous solution was previously autoclaved or filter sterilized. It would be desirable to stabilize formulations of methylnaltrexone such that following the autoclaving process or following storage (or both autoclaving and storage), the amount of the total degradation products would be less than 2.0%, 1.5%, 1.0%, 0.5%, 0.25%, and even 0.125%.

The invention provides stable formulations of methylnaltrexone. By stable solutions of methylnaltrexone, it is meant that following autoclaving at 122 °C, 15 lbs. pressure for 20 minutes, the methylnaltrexone degradation products resulting from such

conditions are not more than 2% of the total methylnaltrexone present in a given solution. By stable solution of methylnaltrexone, it also is meant that following storage of an unautoclaved solution at room temperature for twelve months, the methylnaltrexone degradation products resulting from such conditions are not more than 2% of the total methylnaltrexone present in a given solution. By stable solutions of methylnaltrexone, it is also meant that following storage of an unautoclaved solution at room temperature for two months, the methylnaltrexone degradation products resulting from such conditions are not more than 1.0 % of the total methylnaltrexone present in a given solution. By stable lyophilized formulations of methylnaltrexone, it is meant that following lyophilization and storage at room temperature of methylnaltrexone for two months, and their reconstitution in water the methylnaltrexone degradation products resulting from such conditions are not more than 1.0 % of the total methylnaltrexone present in a given solution.

It was surprisingly discovered that pH alone can solve the problem of excessive methylnaltrexone degradation products. In particular, it was discovered that when the pH of a methylnaltrexone solution containing 2mg/mL of methylnaltrexone was at about 4.25 pH or less, there was a steep drop-off in the amount of methylnaltrexone degradation products following autoclaving. When the pH of the solution containing methylnaltrexone was adjusted to between 3.5 and 4.0, then the total percentage of degradants fell below 2%, and in certain instances even below 1.39%. When the pH was adjusted to between 3.0 and 3.5, the percentage of total degradants dropped to about 0.23% after autoclaving. It was also noted that there was a significant drop, before a plateau, when the pH of the methylnaltrexone solution was brought to below 6.0 prior to autoclaving. Adjusting pHs to between 4.25 and 6 was not sufficient to produce stable formulations of methylnaltrexone (through the adjustment of pH alone). As will be seen below, however, manipulating other parameters in concert with pH resulted in stable formulations of methylnaltrexone anywhere in a range from a pH of 2.0 to 6.0. The benefits of a low pH on the stability of methylnaltrexone formulations persisted in the presence of chelating agents, isotonicity agents, buffering agents, and antioxidants. Thus, the invention in one aspect provides stable formulations of methylnaltrexone in solution, wherein the pH is below 4.25, preferably between 3.0 and 4.0, and most preferably between 3.0 and 3.5.

Applicants also noted that despite setting the pH of a methylnaltrexone solution at points between 3.0 and 6.0 using a pH-adjusting acid or pH-adjusting base prior to autoclaving and despite the benefits obtained from lower pH, the pH of the autoclaved sample drifted almost immediately to about 7.0. It was therefore tested, in particular, whether buffering agents could eliminate the pH drift that resulted from autoclaving without negatively affecting the ability to protect against heat degradation resulting from autoclaving. Applicants discovered that buffering agents indeed could be employed to stabilize the pH of methylnaltrexone solutions throughout the autoclaving process without permitting degradation products to exceed acceptable minimums. Buffers were used in concentrations ranging from 0.25 mM to 25 mM. Acceptable levels of degradation products were obtained at all buffer concentrations tested. It was noted, however, that citrate buffer had properties more desirable than those of acetate buffer. In particular, the addition of citrate buffer did not seem to alter in any material respects the amount of degradation products resulting from autoclaving the methylnaltrexone solution, resulting in less than 0.23% of degradation products at pH of 3.5. The addition of acetate buffer, however, appeared to increase somewhat the amount of methylnaltrexone degradation products, although not to unacceptable levels, resulting in less than 1.39% of degradation products at pH of 3.6. Nonetheless, citrate buffer surprisingly is preferable to acetate buffer. The preferred citrate buffer range is between about 2 and 5 mM.

Buffers in general are well known to those of ordinary skill in the art. Buffer systems include citrate buffers, acetate buffers, borate buffers, and phosphate buffers. Examples of buffers include citric acid, sodium citrate, sodium acetate, acetic acid, sodium phosphate and phosphoric acid, sodium ascorbate, tartartic acid, maleic acid, glycine, sodium lactate, lactic acid, ascorbic acid, imidazole, sodium bicarbonate and carbonic acid, sodium succinate and succinic acid, histidine, and sodium benzoate and benzoic acid.

Applicants also discovered, surprisingly, that a chelating agent alone was capable of reducing the amount of degradation products to acceptable levels. In particular, pH was not adjusted and disodium edetate was added at concentrations of 0.01, 0.1, 0.25, 0.5, 0.75, and 1.0 mg/mL. The disodium edetate stabilized methylnaltrexone against heat degradation in a concentration-dependent manner. As little as 0.01 mg/mL had a

substantial effect on the amount of degradants, yielding approximately 2.3% total degradants. A concentration of 0.1 mg/mL resulted in under 1.5% total degradants. There was a critical point at approximately 0.3 – 0.4 mg/mL where the total degradants became slightly under 0.5% and leveled off with increasing amounts of disodium edetate. Thus, disodium edetate alone was sufficient to render stable an unbuffered solution of methylnaltrexone with no adjustment to pH. This was a surprising result.

Applicants believe that the result is not limited to disodium edetate. Instead, other chelating agents well known to those of ordinary skill in the art will be useful according to the invention. Chelating agents are chemicals which form water soluble coordination compounds with metal ions in order to trap or remove the metal irons from solution, thereby avoiding the degradative effects of the metal ions. Chelating agents include ethylenediaminetetraacetic acid (also synonymous with EDTA, edetic acid, versene acid, and sequestrene), and EDTA derivatives, such as dipotassium edetate, disodium edetate, edetate calcium disodium, sodium edetate, trisodium edetate, and potassium edetate. Other chelating agents include citric acid and derivatives thereof. Citric acid also is known as citric acid monohydrate. Derivatives of citric acid include anhydrous citric acid and trisodiumcitrate-dihydrate. Still other chelating agents include niacinamide and derivatives thereof and sodium desoxycholate and derivatives thereof. A synergistic effect of pH and disodium edetate was also observed. At pH 3 - 3.5, in the presence of citrate buffer (25 mM), and 0.01 mg/mL disodium edetate, the total degradants after autoclaving amounted to less than 0.4%. Under the same conditions, except increasing the concentration of disodium edetate to 1 mg/mL, there was no detectable difference. That is, the degradants were on the order of approximately 0.4% after autoclaving. The circumstance, however, differed when pH was adjusted upwardly to between 6.0 and 7.0 in an unbuffered system. In particular, at a pH adjusted upwardly to between 6.0 and 7.0, the total degradants were above 3 - 6% at a concentration of 0.01 mg/mL disodium edetate and approximately 2.8% at 1.0 mg/mL disodium edetate. This at first glance appears anomalous with the results described above, where disodium edetate alone was sufficient to bring total degradants under 0.5% at concentrations above approximately 0.3 disodium edetate mg/mL. It was discovered, however, that the increase in degradation was due to the addition of a pH-adjusting base to the solution containing methylnaltrexone to upwardly adjust the pH to 6.0 – 7.0. Therefore, it was

discovered unexpectedly that the addition of a pH-adjusting base, such as sodium hydroxide, to a solution containing methylnaltrexone should be avoided in order to minimize the presence of degradants.

The same results were achieved through a combination of acetate buffer and disodium edetate at 0.01 mg/mL and 1.0 mg/mL, although, once again, citrate buffer seemed to work surprisingly better than acetate buffer in protecting methylnaltrexone from heat degradation. Higher levels of disodium edetate in the presence of acetate buffer could compensate, however, for the differential effect that was observed when using citrate buffer versus acetate buffer. It is to be noted that citrate buffer also is a chelating agent, which might contribute to its apparent superior properties. However, there was no concentration-dependent stabilization due to citrate buffer and it would appear that the chelating effect of citrate is not wholly responsible for the differential effects observed between citrate buffer and acetate buffer.

Applicants also believe that antioxidants will be useful according to the invention. Antioxidants are substances capable of inhibiting oxidation by removing free radicals from solution. Antioxidants are well known to those of ordinary skill in the art and include materials such as ascorbic acid, ascorbic acid derivatives (e.g., ascorbylpalmitate, ascorbylstearate, sodium ascorbate, calcium ascorbate, etc.), butylated hydroxy anisole, buylated hydroxy toluene, alkylgallate, sodium meta-bisulfite, sodium bisulfite, sodium dithionite, sodium thioglycollic acid, sodium formaldehyde sulfoxylate, tocopherol and derivatives thereof, (d-alpha tocopherol, d-alpha tocopherol acetate, dl-alpha tocopherol acetate, d-alpha tocopherol succinate, beta tocopherol, delta tocopherol, gamma tocopherol, and d-alpha tocopherol polyoxyethylene glycol 1000 succinate) monothioglycerol, and sodium sulfite. Such materials are typically added in ranges from 0.01 to 2.0%.

The pharmaceutical preparations of the invention also may include isotonicity agents. This term is used in the art interchangeably with iso-osmotic agent, and is known as a compound which is added to the pharmaceutical preparation to increase the osmotic pressure to that of 0.9% sodium chloride solution, which is iso-osmotic with human extracellular fluids, such as plasma. Preferred isotonicity agents are sodium chloride, mannitol, sorbitol, lactose, dextrose and glycerol.

Optionally, the pharmaceutical preparations of the invention may further comprise a preservative. Suitable preservatives include but are not limited to: chlorobutanol (0.3 – 0.9% W/V), parabens (0.01 – 5.0%), thimerosal (0.004 – 0.2%), benzyl alcohol (0.5 – 5%), phenol (0.1 – 1.0%), and the like.

In view of the success achieved with disodium edetate alone in an unbuffered system, it would have been expected that stable formulations could be prepared at virtually any pH simply by optimizing the various potential methylnaltrexone degradation inhibiting agents. Such agents include those as described above, that is, chelating agents, buffering agents, antioxidants, and the like. It was discovered, however, that stable formulations of methylnaltrexone in solution could not be obtained with such degradation inhibiting agents at pHs above 6. Thus, in one aspect of the invention, stable pharmaceutical preparations containing methylnaltrexone in solution are permitted, wherein the solution further includes an agent selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof, provided that the solution has a pH ranging from between 2 to 6.

The stable pharmaceutical preparations of the invention are stable not only to heat degradation resulting from autoclaving, but also to other sterilization processes used during manufacturing. Sterilization processes or techniques as used herein include aseptic techniques such as one or more filtration (0.45 or 0.22 micron filters) steps, autoclaving, and a combination of filtration and autoclaving. They also are stable to long term storage. The stable formulations of the invention are stable for at least six months at temperatures of 30 °C or less, preferably a range from 5 °C to 30 °C, and, more preferably, they are stable at a temperature above 15 °C for at least six months. More particularly, the stable pharmaceutical preparations are stable for periods of at least six months, at least twelve months, and even at least twenty-four months at about room temperature or 25 °C. Such preparations remain substantially free of methylnaltrexone degradation products, that is, such solutions contain less than 2% methylnaltrexone degradation products compared to the total amount of methylnaltrexone in the solution.

Applicants also discovered, surprisingly, that lyophilizing conditions could dramatically affect the amount of methylnaltrexone degradation products. The pharmaceutical preparations of the invention therefore may advantageously include cryoprotective agents, which protect methylnaltrexone from the harmful effects of

freezing. Such agents also can prevent caking and flaking, which can be problematic in reconstituting a solution and in manufacturing processing. Important cryoprotecting agents are mannitol, lactose, sucrose, polyethylene qlycol and polyvinyl pyrrolidine. Most preferred is mannitol. It is believed that cryoprotecting agents which result in a reconstitution pH of 6.0 and higher or which are basic will contribute also to degradation of methylnaltrexone due to pH effects discussed above. Thus, preferred cryoprotecting agents are those which, together with the other components of the formulation, result in a pH in the preferred ranges described above. Preferably, the cryoprotecting agent is neutral or acidic.

The amount of methylnaltrexone in the solution is effective to treat completely, ameliorate, or even prevent conditions associated with activation of endogenous opioid receptors, in particular, peripheral opioid receptors such as mu opioid receptors. Such conditions include nausea, emesis, dysphoria, pruritus, urinary retention, ileus, post-operative ileus, post-partumileus, parallytic ileus, bowel hypomotility, constipation, gastric hypomotility, delayed gastric emptying, decreased biliary secretion, decreased pancreatic secretion, biliary spasm, increased sphincter tone, cutaneous flushing, impaction, sweating, inhibition of gastrointestinal motility, inhibition of gastric emptying, gastrointestinal dysfunction, incomplete evacuation, bloating, abdominal distention, increased gastroesophageal reflux, hypotension, bradycardia, irritable bowel syndrome, or immunosuppression. One important use is in the treatment of constipation, i.e., less than one bowel movement in 3 days or less than 3 bowel movements in a week.

In any of the foregoing embodiments, the methylnaltrexone can be present in an amount sufficient to accelerate discharge from hospital post-surgery, accelerate bowel sounds after surgery, or induce laxation. Such amounts are well known to those of ordinary skill in the art and are described in the literature, including the patents listed in the background of the invention. The methylnaltrexone may also be in a salt form, including the bromide, chloride, iodide, carbonate, and sulfate salts of methylnaltrexone.

Patients treatable with the formulations of the invention include those receiving opioids including opioids for pain, cancer or surgical patients, immunosuppressed or immunocompromised patients (including HIV infected patients), patients with advanced medical illness, terminally ill patients, patients with neuropathies, patients with rheumatoid arthritis, patients with osteoarthritis, patients with chronic pack pain, patients

with spinal cord injury, patients with chronic abdominal pain, patients with chronic pancreatic pain, patients with pelvic perineal pain, patients with fibromyalgia, patients with chronic fatigue syndrome, patients with migraine or tension headaches, patients on hemodialysis, and patients with sickle cell anemia.

The pharmaceutical preparations of the invention also can include an opioid. The therapeutic use of opioids is well known and, again, is described in both the literature and the patents mentioned above. Opioids include alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol.

It should be understood that the pharmaceutical preparations of the invention will typically be held in bottles, vials, ampoules, infusion bags, and the like, any one of which may be sparged to eliminate oxygen or purged with nitrogen. In some embodiments, the bottles vials and ampoules are opaque, such as when amber in color. Such sparging and purging protocols are well known to those of ordinary skill in the art and should contribute to maintaining the stability of the pharmaceutical preparations. The pharmaceutical preparations also, in certain embodiments, are expected to be contained within syringes.

According to another aspect of the invention, kits also are provided. Referring to Figure 3, a kit 10 is depicted. The kit 10 includes a pharmaceutical preparation vial 12, a pharmaceutical preparation diluent vial 14, an opioid vial 16, and an opioid diluent vial 18. The kit also includes instructions 20. The vial 14 containing the diluent for the pharmaceutical preparation is optional. The vial 14 contains a diluent such as physiological saline for diluting what could be a concentrated solution of methylnaltrexone contained in vial 12. The instructions can include instructions for mixing a particular amount of the diluent with a particular amount of the concentrated pharmaceutical preparation, whereby a final formulation for injection or infusion is prepared. The instructions may include instructions for use in a patient controlled analgesia (PCA) device. Likewise, the kit optionally contains an opioid in the opioid

vial 16, which also optionally may be in a concentrated form. The optional vial 18 contains a diluent for a concentrated opioid. The instructions also may include instructions for mixing the opioid with the pharmaceutical preparation and/or diluting the opioid with the opioid diluent contained in the opioid diluent vial 18. The instructions, therefore, would take a variety of forms depending on the presence or absence of diluent and opioid. The instructions 20 can include instructions for treating a patient with an effective amount of methylnaltrexone. It also will be understood that the containers containing the pharmaceutical preparation, whether the container is a bottle, a vial with a septum, an ampoule with a septum, an infusion bag, and the like, can contain indicia such as conventional markings which change color when the pharmaceutical preparation has been autoclaved or otherwise sterilized.

The pharmaceutical preparations of the invention, when used in alone or in cocktails, are administered in therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters discussed below; but, in any event, is that amount which establishes a level of the drug(s) effective for treating a subject , such as a human subject, having one of the conditions described herein. An effective amount means that amount alone or with multiple doses, necessary to delay the onset of, inhibit completely or lessen the progression of or halt altogether the onset or progression of the condition being treated. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

The pharmaceutical preparations of the present invention may include or be diluted into a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid, or semi-solid or liquid fillers, diluants or encapsulating substances which are suitable for administration to a human or other mammal such as a dog, cat, horse, cow, sheep, or goat. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The carriers are capable of

being commingled with the preparations of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy or stability. Carriers suitable for oral, subcutaneous, intravenous, intramuscular, etc. formulations can be found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa.

A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Generally, daily oral doses of active compounds will be from about 0.1 mg/kg per day to 30mg/kg per day. It is expected that IV doses in the range of 0.01 – 1.00 mg/kg will be effective. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous IV dosing over, for example, 24 hours or multiple doses per day also are contemplated to achieve appropriate systemic levels of compounds. Preferred subcutaneous doses for chronic opioid users to induce laxation are 0.1-0.3 mg/kg, and preferred oral doses for the same patient population are 1.0-3.0 mg/kg. Preferred IV doses to treat post operative ileus are 0.15 mg/kg.

The invention also involves methods for preparing autoclaved pharmaceutical preparations that have concentrations of methylnaltrexone degradation products that do not exceed 2% of the methylnaltrexone or salt thereof in the preparation. Aqueous solutions of methylnaltrexone are prepared. A pH-adjusting acid is added to adjust the pH to 4.25 or less, preferably to a range of between 3.0 and 3.5. The solution is then autoclaved according to standard procedures. One such procedure involves autoclaving at 122 °C and 15 pounds of pressure for 20 minutes. The pharmaceutical preparation can contain any one, any combination of or all of a chelating agent, an isotonicity agent, a

buffering agent, an antioxidant, a cryoprotective agent, and an opioid. According to another aspect of the invention, a pharmaceutical preparation containing methylnaltrexone in a aqueous solution is prepared by combining a chelating agent with the methylnaltrexone solution and then autoclaving the solution. The aqueous solution of methylnaltrexone may contain any one of, any combination of or all of a buffering agent, an antioxidant, an isotonicity agent and an opioid.

According to yet another aspect of the invention, a pharmaceutical preparation containing methylnaltrexone in a lyophilized formulation is prepared by combining a cryoprotective agent, such as mannitol, with the methylnaltrexone formulation. The lyophilized preparation may also contain any one of, any combination of, or all of a buffering agent, an antioxidant, an isotonicity agent and an opioid.

The invention also involves methods of inhibiting the formation of methylnaltrexone degradation products in a solution containing methylnaltrexone by combining any one of, any combination of or all of a chelating agent, a buffering agent and an antioxidant with methylnaltrexone or salt thereof in solution. In one preferred embodiment, the aqueous solution containing the chelating agent, buffering agent and/or antioxidant is first prepared, then a powdered source of methylnaltrexone or salt thereof is dissolved into the aqueous solution.

The invention also involves methods of inhibiting the formation of methylnaltrexone degradation products in a gel containing methylnaltrexone by combining any one of, any combination of or all of a chelating agent, a buffering agent and an antioxidant with methylnaltrexone or salt thereof in a gel matrix. In one preferred embodiment, the gel containing the chelating agent, buffering agent and/or antioxidant is first prepared, then a powdered source of methylnaltrexone or salt thereof is dissolved into the gel. As used herein, solution embraces gels.

The pharmaceutical preparations of the invention may be provided in particles. Particles as used herein means nano or microparticles (or in some instances larger) which can consist in whole or in part of the peripheral opioid antagonists or the other therapeutic agent(s) as described herein. The particles may contain the therapeutic agent(s) in a core surrounded by a coating, including, but not limited to, an enteric coating. The therapeutic agent(s) also may be dispersed throughout the particles. The therapeutic agent(s) also may be adsorbed into the particles. The particles may be of any

order release kinetics, including zero order release, first order release, second order release, delayed release, sustained release, immediate release, and any combination thereof, etc. The particle may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, but not limited to, erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the antagonist in a solution or in a semi-solid state. The particles may be of virtually any shape.

Both non-biodegradable and biodegradable polymeric materials can be used in the manufacture of particles for delivering the therapeutic agent(s). Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of time over which release is desired. Bioadhesive polymers of particular interest include bioerodible hydrogels described by H.S. Sawhney, C.P. Pathak and J.A. Hubell in *Macromolecules*, (1993) 26:581-587, the teachings of which are incorporated herein. These include polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

The invention also provides methods for preparing stable pharmaceutical preparations containing aqueous solutions of methylnaltrexone or salts thereof to inhibit formation of methylnaltrexone degradation products. A solution is provided that contains methylnaltrexone or salts thereof and at least one methylnaltrexone inhibiting agent. The solution is processed under at least one sterilization technique prior to and/or after terminal filing the solution in the sealable container to form a stable pharmaceutical preparation, wherein the method is carried out without the addition of a pH-adjusting base to the solution.

EXAMPLES

Example 1

Manufacturing Process for a Pharmaceutical Formulation of Methylnaltrexone

A manufacturing process can be outlined as follows:

1. Add required amount of water for injection (~80% or final volume) to a stainless steel tank.
2. Add chelating agent to the tank and stir till dissolved.
3. Add buffering agent to the tank and stir till dissolved.
4. Add methylnaltrexone to the tank and stir till dissolved.
5. Add isotonicity agent to the tank and stir till dissolved.
6. Adjust the pH of the solution to pH 3.25.
7. Add water for injection to increase the volume to the required amount.
8. Transfer material to supply pressure vessel.
9. Sterile filter into a sterile stainless steel pressure vessel.
10. Fill into bottles/vials, purge with nitrogen and then stopper the bottles/vials.
11. Sterilize the filled vials by autoclaving.

Exact amount of excipients to be used:

Disodium edetate = 0.75 mg/ml	Added in step 2
Sodium Citrate = 0.199 mg/ml	Added in step 3
Citric acid = 0.35 mg/ml	Added in step 3
Sodium Chloride = 8.5 mg/ml	Added in step 5

The order of addition of excipients is described above. Steps 2 to 5 can take place in any order.

When all excipients and drug have been added, step 6, pH of the solution is adjusted by addition of acid. If a buffering agent is used in the solution, pH adjustment may not be required.

There are no specifics on the temperature or the stirring speed during the formulation. The temperature during formulation can be as high as 80 °C.

Example 2

Preferred Manufacturing Process for a Pharmaceutical Formulation of Methylnaltrexone

A preferred manufacturing process is as follows:

100 ml of 20 mg/ml solution of methylnaltrexone solutions

1. Add 80 ml of water for injection (~80% or final volume) to a stainless steel tank.
2. Add 75 mg of disodium edetate, a chelating agent, to the tank and stir till dissolved.
3. Add 19.9 mg of sodium citrate and 35 mg of citric acid (as buffering agents) to the tank and stir till dissolved.
4. Add 2000 mg of methylnaltrexone to the tank and stir till dissolved.
5. Add 850 mg of sodium chloride, an isotonicity agent, to the tank and stir till dissolved.
6. Adjust the pH of the solution if necessary.
7. Add water for injection to increase the volume to 100 ml.
8. Transfer the material to supply pressure vessel.
9. Sterile filter using a 0.22 micron filter into a sterile stainless steel pressure vessel.
10. Fill, purge with nitrogen and then stopper the bottles/vials.
11. Sterilize the filled vials by autoclaving.

Example 3

12 Month Stability of Pharmaceutical Preparation Methylnaltrexone

Methylnaltrexone (bromide salt) and its degradation products in an isotonic saline solution were tested upon manufacture of the solution (no added stabilizers, sterile filtered, not autoclaved) and upon storage at room temperature for 12 months using a Hewlett-Packard HP1100 series, HPLC system equipped with quaternary gradient pump, programmable variable wavelength UV detector and a Millennium data acquisition system. Two mobile phases were prepared as follows:

The reagents, standards and media included naltrexone methobromide as a reference standard, trifluoroacetic acid (ACS grade), acetonitrile (HPLC grade), Milli-Q

water (or equivalent), and methanol (HPLC grade). The solutions were prepared as follows. Mobile phase A (85:15:0.1) (water:methanol:trifluoroacetic acid): 850 mL of Milli-Q water was added to a suitable container, to which 150 mL of methanol and 1.0 mL of trifluoroacetic acid were added. The solution was mixed well and allowed to equilibrate to room temperature. The solution was degassed by helium sparge. Mobile phase B (methanol): Methanol was added to a suitable container and degassed by helium sparge.

Instrumental Conditions

Analytical Column: Metachem Inertsil ODS3, 5µm, 150 x 4.6 mm or equivalent

Mobile phase: A mixture of Mobile phase A and B is used as shown in Table I:

Table I

Time (minutes)	%A	%B
0	100	0
12	65	35
15	35	65
15.1	100	0
20	100	0

Column temperature: 50 °C

Detection: UV at 280 nm

Injection volume: 20 µL

Run time: 20 minutes

Flow rate: 1.5 mL/minute

Quantitation: Peak area responses

Results:

20mg/ml saline drug product lot CTM-02085

Peak No.		Initial		12 months	
		RRT	% Degradants	RRT	% Degradants
1	degradation product	0.72	0.07	0.74	0.25
2	degradation product	0.89	<0.05	0.89	0.72
3	methylnaltrexone	1.00	99.7	1.00	98.6
4	degradation product	1.48	0.06	1.40	0.16
5	O-Methylnaltrexone Bromide (process impurity)	1.57*	0.17	1.54*	0.17

Samples from the methylnaltrexone saline formulation (not autoclaved) were analyzed for methylnaltrexone degradation products before and after storage for 12 months at 25 °C.

The starting material was analyzed by HPLC. As shown in Fig. 1, methylnaltrexone is a peak having an RRT of 1.0 (4.364 minutes). An additional peak was identified as O-methyl naltrexone methobromide, RRT about 1.57 (6.868 minutes). The O-methyl-naltrexone is not a degradant of methylnaltrexone but a result from the methylnaltrexone (drug substance) manufacturing process.

The material stored for 12 months was similarly analyzed by HPLC. The chromatogram is shown in Fig. 2.

As in the starting material, the HPLC analysis of the sample stored for 12 months showed methylnaltrexone RRT of 1.00 (3.839 minutes), O-methyl-methylnaltrexone RRT of about 1.53 (5.866 minutes). However, HPLC analysis revealed that the methylnaltrexone saline formulation which was stored for 12 months had at least three degradation products formed during the manufacturing or during storage of the finished drug product. The degradant peak RRT's were approximately 0.74 (2.828 minutes), 0.89 (3.435 minutes) and 1.40(5.326 minutes).

HPLC analysis was also conducted, prior to storage, on a methylnaltrexone solution manufactured using an isotonic saline solution (no added stabilizers), sterile

filtered, and autoclaved. This saline, autoclaved solution contained the degradation products formed during manufacturing or storage, as described above (data not shown).

Example 4

Preparation of a Subcutaneous Formulation

The degradation products seen with very low citrate level were the same as those seen with normal saline solution. These low citrate formulas were autoclaved and after three months the amount of degradation products seen were less than 0.1% for each degradation product. The formula used for the citrate/EDTA formulation is listed below:

	mg/mL
Methynaltrexone	30mg
Sodium Chloride	4mg
Citric acid	0.0875mg
Trisodium Citrate	0.0496mg
Disodium edetate	0.75mg
Water for injection	q.s. to 1gram

The pH of this solution is 3.5 and can withstand autoclaving process.

Example 5

Manufacturing Process for a Lyophilized Pharmaceutical Formulation of Methylnaltrexone

The lyophilization cycle listed below is standard procude well known to one of ordinary skill in the art. This cycle was used for the preparation of lyophilized preparation of methylnaltrexone analyzed in Examples 6 and 7.

1. Load chamber at room temperature (20-25C)

2. Lower shelf temp to -45 degrees C at 1.0 degrees C/min
3. Hold shelf temp at -45 for 120 minutes
4. When condenser is below -50 degrees C, evacuate the chamber to 100-125 mt.
5. Ramp shelf to -20 degrees C at 0.5 degrees C/min.
6. Hold at -20 degrees C for 16 hours
7. Ramp shelf to +27 degrees C at 0.10 degrees C/min.
8. Hold for a minimum of 8 hours. Maintain chamber pressure at 100-125mt for the entire cycle.
9. Restore chamber to 11.0 PSIA + or- 1.0 with sterile filtered Nitrogen and then seat the

closures (2" Hg), then bleed to atmospheric pressure with Nitrogen to unload.

Example 6

Stability of Lyophilized Formulations of Methylnaltrexone

The following data reports the stability of lyophilized formulations of methylnaltrexone using different cryoprotecting agents.

Cryoprotecting Agent	pH	total degradation products
Mannitol	**5.0**	**0.34%**
Polyvinyl pyrrolidone	**4.1**	**0.37%**
Polyethylene glycol	**5.7**	**0.44%**
Histidine	**7.4**	**0.55%**

Example 7

Stability of Lyophilized Formulations of Methylnaltrexone

The following data reports the stability of lyophilized formulations of methylnaltrexone in comparison to buffered formulations.

Amount of total related substances at various stages of manufacturing

	1	2	3	4	5	6
Key Ingredient	Monothio-glycerol	Citrate Buffer pH 3.5	Citrate Buffer pH 5	Acetate Buffer pH 3.6	Lyophilized using Mannitol	Lyophilized using Lactose
Unautoclaved	0.13	0.12	0.16	0.20	0.14	0.12
Autoclaved	0.91	0.23	0.61	1.39	n/a	n/a
Stability (2 mths at room temp)	1.10	0.16	0.48	1.26	0.15	0.15

It should be understood that various changes and modifications to the preferred embodiments described herein will be apparent to those of ordinary skill in the art. Such changes and modifications can be made without departing from the spirit and scope of this invention without diminishing its advantages. It is therefore intended that such changes and modifications, including equivalents, be covered by the appended claims. All of the patents, patent applications and references listed herein are incorporated by reference in their entirety.

CLAIMS

1. A stable pharmaceutical preparation comprising methylnaltrexone or a salt thereof, wherein:

(a) the preparation is an aqueous formulation and the concentration of methylnaltrexone degradation products in the preparation does not exceed 2% of the methylnaltrexone or salt thereof after

i) autoclaving, or

ii) storage at about room temperature,

(b) the preparation is an aqueous formulation and the preparation has a pH below 4.25,

(c) the preparation is an aqueous formulation and the preparation further comprises a chelating agent in an amount such that the preparation after autoclaving has a concentration of methylnaltrexone degradation products that does not exceed 0.5% of the methylnaltrexone or salt thereof in the preparation,

(d) the preparation is an aqueous formulation and the preparation further comprises at least one methylnaltrexone degradation inhibiting agent selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof, wherein the preparation has a pH ranging from 2 to 6, wherein the preparation is processed under at least one sterilization technique, and wherein the preparation has a concentration of methylnaltrexone degradation products that is less than 1.5%, 1.0%, 0.5%, 0.25% or 0.125%, and/or

(e) the preparation is a lyophilised formulation of methylnaltrexone, wherein the formulation upon reconstitution in water at a concentration of 20 mg/ml has a pH of between 2 and 6, or 3 and 5, and optionally includes a cryoprotecting agent in an amount sufficient to render the formulation stable.

2. The pharmaceutical preparation of claim 1, further comprising a degradation inhibiting agent selected from the group consisting of chelating agents, buffering agents, anti-oxidants and combinations thereof, wherein the degradation inhibiting agent is present in an amount sufficient to render stable an aqueous formulation comprising the preparation and containing a concentration of 20 mg/ml methylnaltrexone.

3. The pharmaceutical preparation of claim 1 or 2, wherein the concentration of methylnaltrexone degradation products is less than 1.5%, 1.0%, 0.5%, 0.25% or 0.125%.

4. The pharmaceutical preparation of any one of claims 1 to 3, wherein said storage is for a period of 6 months, 12 months or 2 years.

5. The pharmaceutical preparation of any of the preceding claims, which comprises a chelating agent, optionally EDTA, citric acid, niacinamide, sodium desoxycholate or a derivative of any of the foregoing.

6. The pharmaceutical preparation of claim 5, wherein the chelating agent is EDTA or a derivative thereof, optionally disodium edetate, and is optionally present in a concentration ranging from 0.4 to 100 mg/ml, 0.001 to 100.0 mg/ml, 0.05 to 25.0 mg/ml, 0.1 to 2.5 mg/ml, 0.5 to 25.0 mg/ml, 0.5 to 10.0 mg/ml, 0.5 to 2.5 mg/ml, or 0.5 to 0.75 mg/ml.

7. The pharmaceutical preparation of any of the preceding claims, comprising a buffering agent, optionally citric acid, sodium citrate, sodium acetate, acetic acid, sodium phosphate, phosphoric acid, sodium ascorbate, tartartic acid, maleic acid, glycine, sodium lactate, lactic acid, ascorbic acid, imidazole, sodium bicarbonate, carbonic acid, sodium succinate, succinic acid, histidine, sodium benzoate or benzoic acid.

8. The pharmaceutical preparation of claim 7, comprising citrate buffer, optionally present in a concentration ranging from 0.001 mM to 100 mM, 0.01 to 100.0 mM, 0.01 mM to 50 mM, 0.10 mM to 25 mM, 0.10 to 10.0 mM,or 0.10 to 5.0 mM.

9. The pharmaceutical preparation of any one of the preceding claims, wherein a)

the pH of the preparation does not exceed 4.25 and optionally ranges from 2.0 to 4.0, 2.75 to 4.25, 3.0 to 4.0, or 3.0 to 3.5; and/or

b) the pH is adjusted with HCl, citric acid, sulphuric acid, acetic acid, or phosphoric acid.

10. The pharmaceutical preparation of any one of the preceding claims, wherein the concentration of methylnaltrexone or salt thereof ranges from 0.01 to 100 mg/ml, 0.05 to 100 mg/ml, 0.1 to 100.0 mg/ml, 25 to 75 mg/ml, 1.0 to 50.0 mg/ml, 1 to 20 mg/ml or 0.05 to 0.5 mg/ml, or is about 50 mg/ml, 10.0 mg/ml, or 0.1 mg/ml.

11. The pharmaceutical preparation of any one of the preceding claims, further comprising:

a) an antioxidant, optionally an ascorbic acid derivative, butylated hydroxy anisole, butylated hydroxy toluene, alkyl gallate, sodium meta-bisulfite, sodium bisulfite, sodium dithionite, sodium thioglycollic acid, sodium formaldehyde sulfoxylate, tocopherol or a derivative thereof, monothioglycerol, or sodium sulfite;

b) an isotonicity agent, optionally sodium chloride, mannitol, lactose, dextrose, sorbitol, or glycerol;

c) an opioid, optionally alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, or tramadol; and/or

d) a cryoprotective agent, optionally a polyol or mannitol.

12. The pharmaceutical preparation of any one of the preceding claims wherein the aqueous formulation is provided in a) a vial or ampoule with a septum, b) a syringe, infusion bag or sealable bottle, or c) a container including indicia indicating that the pharmaceutical preparation has been autoclaved.

13. Use of the pharmaceutical preparation as claimed in any of the preceding claims for the manufacture of a medicament for treating a side effect associated with opioid treatment.

14. Use as claimed in claim 13, wherein the side effect is constipation.

15. A pharmaceutical preparation comprising methylnaltrexone, sodium chloride, citric acid, trisodium citrate and disodium edetate.

16. The pharmaceutical preparation of claim 15, wherein the preparation is an aqueous formulation and the methylnaltrexone is present at between 20 and 40 mg/ml, the sodium chloride is present between 2 and 6 mg/ml, the citric acid is present between 0.05 and 0.1 mg/ml, the trisodium citrate is present between 0.025 and 0.075 mg/ml and the disodium edetate is present between 0.5 and 1.0 mg/ml.

17. A method of producing a pharmaceutical preparation comprising methylnaltrexone or a salt thereof, which is stable to the formation of methylnaltrexone degradation products, the method comprising:

providing an aqueous formulation of methylnaltrexone or a salt thereof, the aqueous formulation being substantially free of methylnaltrexone degradation products and:

i) having a pH of 4.25 or less, and/or

ii) further comprising a chelating agent, buffering agent, and/or an antioxidant,

and optionally autoclaving the aqueous formulation.

18. The method of claim 17, wherein the aqueous formulation includes a chelating agent, buffering agent, and/or antioxidant and the method further comprises adjusting with an acid the pH of the aqueous formulation or the preparation to a pH ranging from 2 to 6, 2 to 5, 3 to 5, or 3 to 4.

19. The method of claim 17 or 18, wherein the pH of the aqueous formulation or preparation ranges from 2.0 to 4.0, 3.0 to 4.0, or 3.0 to 3.5.

20. The method of any of claims 17 to 19, wherein the aqueous formulation contains a chelating agent, an isotonicity agent, optionally sodium chloride, a buffering agent, optionally a citrate buffer, an antioxidant and/or a cryoprotecting agent, optionally a polyol.

21. The method of claim 20, wherein the chelating agent is EDTA or derivative thereof, optionally present in a concentration ranging from 0.001 to 100.0 mg/ml, 0.05 to 25.0 mg/ml, or 0.1 to 2.5 mg/ml.

22. The method of any of claims 17 to 21, further comprising lyophilising the aqueous formulation and/or processing the aqueous formulation under a sterilization technique, optionally by autoclaving.

23. The method of any of claims 17 to 22, wherein the concentration of methylnaltrexone degradation products in the preparation is less than 2.0 %, 1.0 %, 0.5 % or 0.25 % of the total methylnaltrexone in the preparation.

24. The method of any of claims 17 to 23, further comprising adding to the aqueous formulation at least one opioid, wherein said opioid, optionally, is:

a) alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine or tramadol; and/or

b) solubilized in a nonaqueous solvent, optionally an oil, wax or alcohol, prior to addition to the aqueous formulation.

25. A pharmaceutical preparation, optionally according to any one of claims 1 to 12, 15 or 16, prepared or preparable by the method as claimed in any one of claims 17 to 24.

26. A kit comprising a package containing a sealed container comprising the pharmaceutical preparation of claim 1 to 12, 15 or 16, and instructions for use.

27. The kit of claim 26, further comprising a diluant container containing a pharmaceutically acceptable diluant, wherein: a) the diluant is a 5% dextrose solution or a physiological saline solution; b) the diluant is contained in a sealable bottle or an infusion bag; and/or c) the kit further comprises instructions for mixing the preparation and diluant.

28. The kit of claim 26 or 27, further comprising an opioid in a container, wherein the opioid is optionally alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine or tramadol.

29. A product comprising a lyophilised formulation of methylnaltrexone prepared from an aqueous formulation comprising a pharmaceutical preparation as claimed in any of claims 1-12 and 15.