(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 April 2014 (17.04.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/057365 Al

(51) International Patent Classification:
A61K 9/08 (2006.01) *A61K 31/137* (2006.01)
A61K 47/02 (2006.01)

(21) International Application Number:
PCT/IB2013/053520

(22) International Filing Date:
3 May 2013 (03.05.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2934/MUM/2012 8 October 2012 (08.10.2012) IN

(71) Applicant: **WOCKHARDT LIMITED** [IN/IN]; D-4, MIDC Area, Chikalthana, Aurangabad 431210 (IN).

(72) Inventors: **GUPTA, Amit;** House No. 906, Sector 16, Haryana, Faridabad 121002 (IN). **NAGORI, Rajendra Nandlal;** B-2, Srushtivihar Housing Soc, Zambad Estate, New Shreya Nagar, Aurangabad 431210 (IN). **MERWADE, Arvind Yekanathsa;** Rajendra Prasad Road, Gadag Betgeri - 582102, Karnataka, Belgaum 582102 (IN). **DEO, Keshav;** #A-52, Pranahuti, Narayan Garden, Opp. Yash Complex, Gotri Road., Gujarat, Vadodara 390021 (IN). **JAIN, Girish Kumar;** 4-Sharda Niketan, Teachers' Colony, Pitam Pura, Delhi 110 034 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2014/057365 A1

(54) Title: STABLE INJECTABLE PHARMACEUTICAL COMPOSITION OF EPINEPHRINE OR SALTS THEREOF

(57) Abstract: The present invention refers to a stabilized injectable pharmaceutical composition of epinephrine or salts thereof comprising sodium metabisuliite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisuliite in the composition ranges from about 1 :0.005 to about 1:1.5 by weight. It has been observed that stable injectable epinephrine compositions with excellent storage stability and substantially free of overages can be prepared using sodium metabisuliite in said ratios. Particularly, it was found that using sodium metabisuliite in said ratios controls levels of adrenaline sulfonate impurity in said pharmaceut-

STABLE INJECTABLE PHARMACEUTICAL COMPOSITION OF EPINEPHRINE OR SALTS THEREOF

Field Of The Invention

The present invention relates to a stabilized injectable pharmaceutical composition of epinephrine or salts thereof comprising sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5 by weight. It has been observed that stable injectable epinephrine compositions with excellent storage stability and substantially free of overages can be prepared using sodium metabisulfite in said ratios. Particularly, it was found that using sodium metabisulfite in said ratios controls levels of adrenaline sulfonate impurity in said pharmaceutical compositions.

Background Of The Invention

Epinephrine, also known as adrenaline, is a sympathomimetic catecholamine. Chemically, epinephrine is B-(3, 4dihydroxyphenyl)-a-methyl-amino ethanol.

Epinephrine is the drug of choice for the initial treatment of anaphylaxis. Many epinephrine products are commerically available currently. For instance, epinephrine is marketed in the United States in the form of intramuscular and subcutaneous injection under trade name Twinject®, Auvi-Q®, EpiPen® Auto-Injector, which contains 0.3 mg epinephrine, and EpiPen® Jr Auto-Injector, which contains 0.15mg epinephrine.

It is well known in the art that there is an issue with potency of epinephrine (both in free base form and ionic form) when used in presence of oxygen and free radicals i.e degradation of epinephrine is accelerated in the presence of oxygen and free radicals.

Numerous studies have been conducted to address the effect of formulation variables on the epinephrine degradation kinetics, and attempts have been made to improve the formulation stability.

U.S. Patent No. 3,149,035 discloses use of bisulphite and boric acid to enhance stability of the catechol amines.

U.S. Patent No. 3,966,905 discloses catecholamine solutions at mild pH are suitable for physiological use.

Several literatures suggests that there is an increase in stability of epinephrine when stored in gas-tight containers with an inert gas (e.g. nitrogen) purging, and/or limiting or protecting the epinephrine formulation from direct light exposure or storing in a secondary opaque package. Inspite of using sodium metabisulfite controlling the degradation of epinephrine however continues to be an issue. In addition, interaction of sodium metabisulfite with epinephrine further leads to complications.

Currently marketed products of epinephrine as discussed above includes sodium metabisulfite as an antioxidant as it prevents degradation of the product due to oxidation that may take place during manufacturing, filling, storage, and environmental influence on the formulation.

Currently marketed products of epinephrine i.e EpiPen® Auto-Injector containing 0.3 mg epinephrine and EpiPen® Jr Auto-Injector containing 0.15 mg of epinephrine comprises of same amount of sodium metabisulfite i.e. 0.5 mg. It is also observed that EpiPen® Jr Auto-Injector product generally degrades relatively faster than that in EpiPen® Auto-Injector, presumably due to exposure of the product to substantial vacant space left in the cartridge.

Moreover, Currently marketed products of epinephrine i.e the EpiPen® Auto-Injector products contains more than about 20% of the epinephrine overages. This is in order to compensate the amount of epinephrine degraded during manufacture or over storage. Such overages however, may either lead to undesirable side effects due to dose inaccuracy or generate more degradation products in the product.

Further, currently marketed products contain 0.3mg or 0.15mg in 2.0ml solution, of which only 0.3ml is injected and rest 1.7ml is discarded, which leads to lots of wastage.

Since said product is used in severe anaphylactic reactions, so controlling impurities and improvement of stability is critical. Hence, there exists an enduring need for improved and stable pharmaceutical composition of epinephrine, which exhibits excellent storage stability and does not require addition of epinephrine overages.

Summary Of The Invention

In one aspect, the present invention provides a stabilized injectable pharmaceutical composition comprising epinephrine or salt thereof and sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5by weight.

In another aspect, the present invention provides a stabilized injectable pharmaceutical composition comprising epinephrine or salt thereof and sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5 by weight characterized in that said composition contains epinephrine having purity equal to or greater than 98%.

In another aspect, the present invention provides a stabilized injectable pharmaceutical composition comprising epinephrine or salt thereof and sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5 by weight characterized in that said composition contains total impurity of 4% or less.

In another aspect, the present invention provides a stabilized injectable pharmaceutical composition comprising epinephrine or salt thereof and sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5 by weight characterized in that said composition contains no single impurity of greater than 3%.

In another aspect, the present invention provides a stabilized injectable pharmaceutical composition comprising epinephrine or salt thereof and sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5 by weight characterized in that said composition contains adrenaline sulfonate impurity of about 3.0% or less at RRT 0.15.

In another aspect, the present invention provides a stabilized injectable pharmaceutical composition comprising epinephrine or salt thereof and sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5 by weight characterized in that said composition contains noradrenaline impurity of about 0.1 % or less.

In another aspect, the present invention provides a stabilized injectable pharmaceutical composition comprising epinephrine or salt thereof and sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5 by weight characterized in that said composition contains adrenalone impurity of about 0.5% or less.

In another aspect, the present invention provides a stabilized injectable pharmaceutical composition comprising epinephrine or salt thereof and sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5 by weight characterized in that said composition contains N-benzyl adrenalone impurity of about 0.1 % or less.

In another aspect, the present invention provides a stabilized injectable pharmaceutical composition comprising epinephrine or salt thereof and sodium metabisulfite, wherein the ratio of the amount of epinephrine or salt thereof to sodium metabisulfite in the composition ranges from about 1:0.005 to about 1:1.5 by weight characterized in that said composition contains impurity observed at RRT 0.17, RRT 0.2, or RRT 0.73 of about 0.5% or less.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.