Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiffs
Boehringer Ingelheim Pharmaceuticals, Inc.
and Boehringer Ingelheim International GmbH

Of Counsel:

Christopher N. Sipes
R. Jason Fowler
Eric R. Sonnenschein
Sarahi Uribe
Justin W. Burnam
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street NW
Washington, DC 20001-4956
(202) 662-6000

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. and BOEHRINGER INGELHEIM INTERNATIONAL GMBH, **Plaintiffs,** **v.** **ANOBRI PHARMACEUTICALS US, LLC, NANCHANG ANOVENT PHARMACEUTICAL CO., LTD., and SHANGHAI ANOVENT PHARMACEUTICAL CO., LTD.,** **Defendants.**	**Civil Action No. _____** **(Filed Electronically)**

COMPLAINT FOR PATENT INFRINGEMENT

Boehringer Ingelheim Pharmaceuticals, Inc. and Boehringer Ingelheim International GmbH (collectively, "Boehringer"), by their undersigned attorneys, bring this action against Anobri Pharmaceuticals US, LLC, NanChang Anovent Pharmaceutical Co., Ltd., and Shanghai Anovent Pharmaceutical Co., Ltd. (collectively, "Defendants"), and hereby allege as follows:

NATURE OF THE ACTION

1. This action for patent infringement, brought pursuant to the patent laws of the United States, 35 U.S.C. § 1, *et seq*., and in particular under 35 U.S.C §§ 271 (a–c and e), arises from Defendants' submission of Abbreviated New Drug Application (ANDA) No. 218956 to the United States Food and Drug Administration (FDA). Through this ANDA, Defendants seek approval to market a generic version of the pharmaceutical product STIOLTO® Respimat® prior to the expiration of United States Patent Nos. 7,396,341 ("the '6,341 patent"), 9,027,967 ("the '967 patent"), 7,837,235 ("the '235 patent"), and 8,733,341 ("the '3,341 patent") (collectively, "the patents-in-suit"). Boehringer seeks injunctive relief against infringement, attorneys' fees, and any other relief the Court deems just and proper.

2. This is also an action under 28 U.S.C. §§ 2201 and 2202 for a declaratory judgment of patent infringement arising under the patent laws of the United States, 35 U.S.C. §§ 1, *et seq.*, and, in particular, under 35 U.S.C. § 271.

THE PARTIES

3. Boehringer Ingelheim Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 900 Ridgebury Road, Ridgefield, Connecticut 06877.

4. Boehringer Ingelheim International GmbH is a private limited liability company organized and existing under the laws of Germany, having a principal place of business at Binger Strasse 173, 55216 Ingelheim, Germany.

5. On information and belief, Shanghai Anovent Pharmaceutical Co., Ltd. is a corporation organized and existing under the laws of China, having a place of business at 3rd Floor, Block B, Building 3, No. 299 Kangwei Road, Kangqiao Town, Pudong District, Shanghai, 2000, China.

6. On information and belief, NanChang Anovent Pharmaceutical Co., Ltd. is a corporation organized and existing under the laws of China, having a place of business at Building B1, Lianbo Science and Technology Park, 888 Jingkai Avenue, Nanchang Economic and Technological Development District, NanChang City, 330013 Jiangxi Province, China.

7. On information and belief, NanChang Anovent Pharmaceutical Co., Ltd. is a subsidiary of Shanghai Anovent Pharmaceutical Co., Ltd.

8. On information and belief, Anobri Pharmaceuticals US, LLC is a limited liability company organized and existing under the laws of Delaware, having its principal place of business at One Gateway Center, Suite 2600, Newark, New Jersey 07102. On information and belief, Anobri Pharmaceuticals US, LLC amended its certificate of formation on July 23, 2021, to identify this address as the location of its principal office, and Anobri Pharmaceuticals US, LLC has since used this address in patent assignments recorded at the U.S. Patent and Trademark Office (USPTO), including as recently as June 13, 2023.

9. On information and belief, Anobri Pharmaceuticals US, LLC is a wholly owned subsidiary of NanChang Anovent Pharmaceutical Co., Ltd.

10. On information and belief, Anobri Pharmaceuticals US, LLC, in collaboration with NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd., prepared and submitted ANDA No. 218956 ("Defendants' ANDA"), and they continue to collaborate in seeking FDA approval of Defendants' ANDA.

11. On information and belief, Defendants intend to commercially manufacture, market, offer for sale, and sell the product described in Defendants' ANDA (the "ANDA Product") throughout the United States, including in the State of New Jersey, in the event FDA approves Defendants' ANDA.

JURISDICTION AND VENUE

12. This civil action for patent infringement arises under the patent laws of the United States, including 35 U.S.C. § 271, and alleges infringement of the patents-in-suit. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338, and 2201–02.

13. On information and belief, this Court has personal jurisdiction over Anobri Pharmaceuticals US, LLC because it is a limited liability company with a principal place of business in New Jersey and is the agent of NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd. On information and belief, Anobri Pharmaceuticals US, LLC is acting as the agent of NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd. with respect to Defendants' ANDA.

14. On information and belief, this Court has personal jurisdiction over NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd. because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met: (a) Boehringer's claims arise under federal law; (b) NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd. are foreign defendants not subject to general personal jurisdiction in the courts of any state; and (c) NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd. have sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products to be distributed throughout the United States, such that this Court's exercise of jurisdiction over NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd. satisfies due process.

15. On information and belief, this Court also has jurisdiction over Defendants because, *inter alia*, this action arises from actions of Defendants directed toward New Jersey and because

Defendants have purposefully availed themselves of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with New Jersey. On information and belief, Anobri Pharmaceuticals US, LLC has a principal place of business at One Gateway Center, Suite 2600, Newark, New Jersey 07102. On information and belief, Anobri Pharmaceuticals US, LLC amended its certificate of formation on July 23, 2021, to identify this address as the location of its principal office, and Anobri Pharmaceuticals US, LLC has since used this address in patent assignments recorded at the USPTO, including as recently as June 13, 2023. Anobri Pharmaceuticals US, LLC also represented to the USPTO that it was incorporated in New Jersey, at this address, during the time that Defendants were developing the ANDA Product.

16. On information and belief, Defendants have committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement that will lead to foreseeable harm and injury to Boehringer, which manufactures STIOLTO® Respimat® for sale and use throughout the United States, including this Judicial District. On information and belief, Anobri Pharmaceuticals US, LLC has submitted, caused to be submitted, or aided and abetted in the preparation or submission of Defendants' ANDA, including activities undertaken from One Gateway Center, Suite 2600, Newark, New Jersey 07102. On information and belief, in the event that FDA approves Defendants' ANDA, Anobri Pharmaceuticals US, LLC, with the participation of NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd., intends to commercially manufacture, import, market, offer for sale, and sell the ANDA Product throughout the United States and in this Judicial District.

17. At least because, on information and belief, Anobri Pharmaceuticals US, LLC has a regular and established place of business in New Jersey, committed act(s) of infringement in New Jersey, and is acting as the agent of NanChang Anovent Pharmaceutical Co., Ltd. and

Shanghai Anovent Pharmaceutical Co., Ltd., venue is proper in this Judicial District as to Anobri Pharmaceuticals US, LLC pursuant to 28 U.S.C. § 1400(b).

18. At least because, on information and belief, NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd. are foreign corporations, venue is proper in this Judicial District as to NanChang Anovent Pharmaceutical Co., Ltd. and Shanghai Anovent Pharmaceutical Co., Ltd. pursuant to 28 U.S.C. §§ 1391(c)(3) and 1400(b).

19. Anobri Pharmaceuticals US, LLC has not disputed venue or jurisdiction in this Judicial District in *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Anobri Pharmaceuticals US, LLC, et al.*, Civil Action No. 2:23-cv-03530-CCC-LDW (consolidated), in which Boehringer has accused Anobri of infringing the patents-in-suit on the ground that Anobri seeks approval to market generic versions of SPIRIVA® Respimat® and COMBIVENT® Respimat®.

BOEHRINGER'S APPROVED STIOLTO® RESPIMAT® DRUG PRODUCT AND PATENTS-IN-SUIT

20. Boehringer makes and sells STIOLTO® Respimat®, a product that is a combination of an anticholinergic agent and a long-acting beta$_2$-adrenergic agonist, and that is indicated for the long-term, once-daily maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). A true and correct copy of the prescribing label for STIOLTO® Respimat® is attached hereto as Exhibit A.

21. Boehringer Ingelheim Pharmaceuticals, Inc. is the holder of New Drug Application (NDA) No. 206756 for STIOLTO® Respimat® and a licensee of the patents-in-suit. FDA first approved NDA No. 206756 for STIOLTO® Respimat® in May 2015.

22. Boehringer Ingelheim International GmbH owns the '6,341 patent, which is listed in the Orange Book for STIOLTO® Respimat®.

23. The ’6,341 patent is entitled “Blocking Device for a Locking Stressing Mechanism having a Spring-Actuated Output Drive Device” and was duly and lawfully issued by the USPTO on July 8, 2008. The ’6,341 patent is attached hereto as Exhibit B.

24. Boehringer Ingelheim International GmbH owns the ’967 patent, which is listed in the Orange Book for STIOLTO® Respimat®.

25. The ’967 patent is entitled “Device for Clamping a Fluidic Component” and was duly and lawfully issued by the USPTO on May 12, 2015. The ’967 patent is attached hereto as Exhibit C.

26. Boehringer Ingelheim International GmbH owns the ’235 patent, which is listed in the Orange Book for STIOLTO® Respimat®.

27. The ’235 patent is entitled “Device for Clamping a Fluidic Component” and was duly and lawfully issued by the USPTO on November 23, 2010. The ’235 patent is attached hereto as Exhibit D.

28. Boehringer Ingelheim International GmbH owns the ’3,341 patent, which is listed in the Orange Book for STIOLTO® Respimat®.

29. The ’3,341 patent is entitled “Atomizer and Method of Atomizing Fluid with a Nozzle Rinsing Mechanism” and was duly and lawfully issued by the USPTO on May 27, 2014. The ’3,341 patent is attached hereto as Exhibit E.

30. Boehringer Ingelheim International GmbH owns additional patents that are listed in the Orange Book for STIOLTO® Respimat® for which Defendants have not provided a Paragraph IV certification (“Unchallenged Patents”). Defendants do not seek approval to market a generic version of STIOLTO® Respimat® prior to expiration of the Unchallenged Patents, including any associated pediatric exclusivity. The Unchallenged Patents are: (i) U.S. Patent

No. 7,284,474, entitled "Piston-Pumping System Having O-Ring Seal Properties," which expired on August 26, 2024, but benefits from pediatric exclusivity until February 26, 2025; (ii) U.S. Patent No. 7,896,264, entitled "Microstructured High Pressure Nozzle with Built-in Filter Function," which expires on May 26, 2025; (iii) U.S. Patent No. 7,220,742, entitled "Enantiomerically Pure Beta Agonists, Process for the Manufacture Thereof and Use Thereof as Medicaments," which expires on May 12, 2025; (iv) U.S. Patent No. 7,727,984, entitled "Medicaments for the Treatment of Chronic Obstructive Pulmonary Disease," which expires on January 19, 2027; and (v) U.S. Patent No. 8,034,809, entitled "Enantiomerically Pure Beta Agonists, Process for the Manufacture Thereof and Use Thereof as Medicaments," which expires on May 12, 2025.

31. Thus, Defendants do not seek final FDA approval to market a generic version of STIOLTO® Respimat® prior to January 19, 2027.

DEFENDANTS' ANDA

32. On information and belief, Defendants have submitted or caused to be submitted Defendants' ANDA to FDA under 21 U.S.C. § 355(j), in order to obtain approval to engage in the commercial manufacture, use, or sale of tiotropium bromide and olodaterol hydrochloride inhalation spray as a purported generic version of STIOLTO® Respimat® prior to the expiration of the patents-in-suit.

33. On information and belief, on or about July 30, 2024, Defendants mailed Boehringer a letter regarding "notice and information required by 21 U.S.C. §§ 355(j)(2)(B)(i) and (ii)" ("Notice Letter"). The Notice Letter represented that Defendants had submitted to FDA Defendants' ANDA and a purported Paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of the product described in Defendants' ANDA before the expiration of the patents-in-suit, which are listed in the Orange Book for STIOLTO® Respimat®.

Hence, Defendants' purpose in submitting Defendants' ANDA is to manufacture and market the ANDA Product before the expiration of the patents-in-suit.

34. Defendants' Notice Letter contained a purported offer of confidential access ("Defendants' Offer"). Pursuant to Defendants' Offer, Defendants produced only limited information about the proposed inhaler from Defendants' ANDA. Specifically, Defendants produced only a single, 19-page document from their ANDA. Defendants thus have not provided reasonable access to Defendants' ANDA, and Defendants' actions have impeded Boehringer's ability to evaluate Defendants' contentions that the proposed inhaler does not infringe certain of the patents-in-suit.

35. Upon information and belief, the inhaler device of Defendants' ANDA is the same as the device at issue in *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Anobri Pharmaceuticals US, LLC, et al.*, Civil Action No. 2:23-cv-03530-CCC-LDW (consolidated).

36. On information and belief, Defendants have participated in the preparation and submission of Defendants' ANDA, have provided material support to the preparation and submission of Defendants' ANDA, and intend to support the further prosecution of Defendants' ANDA.

37. On information and belief, if FDA approves Defendants' ANDA, Defendants will manufacture, offer for sale, or sell the ANDA Product within the United States, including within New Jersey, or will import the ANDA Product into the United States, including New Jersey.

38. Alternatively, on information and belief, if FDA approves Defendants' ANDA, Defendants will actively induce or contribute to the manufacture, use, offer for sale, or sale of the ANDA Product within the United States, including within New Jersey, or will import the ANDA Product into the United States, including New Jersey. On information and belief, Defendants'

ANDA Product is especially adapted for a use that infringes one or more claims of the patents-in-suit and there is no substantial noninfringing use for Defendants' ANDA Product.

39. This action is being filed within forty-five days of Boehringer's receipt of the Notice Letter, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

COUNT I
INFRINGEMENT OF THE '6,341 PATENT

40. Boehringer incorporates by reference paragraphs 1–39 as if fully set forth herein.

41. On information and belief, Defendants have submitted or caused the submission of Defendants' ANDA to FDA and continue to seek FDA approval of Defendants' ANDA.

42. Defendants have infringed the '6,341 patent under 35 U.S.C. § 271(e)(2)(A) by submitting Defendants' ANDA with a Paragraph IV certification and seeking FDA approval of Defendants' ANDA prior to the expiration of the '6,341 patent.

43. On information and belief, if Defendants' ANDA is approved, Defendants and their affiliates will make, offer for sale, sell, import, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing one or more claims of the '6,341 patent.

44. Defendants' commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to the infringement of the '6,341 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 218956, Defendants will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '6,341 patent.

45. Defendants had actual knowledge of the '6,341 patent prior to submitting Defendants' ANDA and were aware that the submission of Defendants' ANDA with the request for FDA approval prior to the expiration of the '6,341 patent would constitute an act of infringement of the '6,341 patent. Defendants had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not directly infringe, contribute to the infringement of, and/or induce the infringement of the '6,341 patent.

46. In addition, Defendants submitted Defendants' ANDA without adequate justification for asserting the '6,341 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Defendants' conduct in certifying invalidity, unenforceability, and/or noninfringement with respect to the '6,341 patent thus renders this case "exceptional" under 35 U.S.C. § 285.

47. Boehringer will be irreparably harmed if Defendants are not enjoined from infringing and from actively inducing or contributing to the infringement of the '6,341 patent. Boehringer does not have an adequate remedy at law and, considering the balance of hardships between Boehringer and Defendants, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT II
INFRINGEMENT OF THE '967 PATENT

48. Boehringer incorporates by reference paragraphs 1–47 as if fully set forth herein.

49. On information and belief, Defendants have submitted or caused the submission of Defendants' ANDA to FDA and continue to seek FDA approval of Defendants' ANDA.

50. Defendants have infringed the '967 patent under 35 U.S.C. § 271(e)(2)(A) by submitting Defendants' ANDA with a Paragraph IV certification and seeking FDA approval of Defendants' ANDA prior to the expiration of the '967 patent.

51. On information and belief, if Defendants' ANDA is approved, Defendants and their affiliates will make, offer for sale, sell, import, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing one or more claims of the '967 patent.

52. Defendants' commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to the infringement of the '967 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 218956, Defendants will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '967 patent.

53. Defendants had actual knowledge of the '967 patent prior to submitting Defendants' ANDA and were aware that the submission of Defendants' ANDA with the request for FDA approval prior to the expiration of the '967 patent would constitute an act of infringement of the '967 patent. Defendants had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not directly infringe, contribute to the infringement of, and/or induce the infringement of the '967 patent.

54. In addition, Defendants submitted Defendants' ANDA without adequate justification for asserting the '967 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Defendants' conduct in certifying invalidity, unenforceability, and/or noninfringement with respect to the '967 patent thus renders this case "exceptional" under 35 U.S.C. § 285.

55. Boehringer will be irreparably harmed if Defendants are not enjoined from infringing and from actively inducing or contributing to the infringement of the '967 patent. Boehringer does not have an adequate remedy at law and, considering the balance of hardships between Boehringer and Defendants, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT III
INFRINGEMENT OF THE '235 PATENT

56. Boehringer incorporates by reference paragraphs 1–55 as if fully set forth herein.

57. On information and belief, Defendants have submitted or caused the submission of Defendants' ANDA to FDA and continue to seek FDA approval of Defendants' ANDA.

58. Defendants have infringed the '235 patent under 35 U.S.C. § 271(e)(2)(A) by submitting Defendants' ANDA with a Paragraph IV certification and seeking FDA approval of Defendants' ANDA prior to the expiration of the '235 patent.

59. On information and belief, if Defendants' ANDA is approved, Defendants and their affiliates will make, offer for sale, sell, import, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing one or more claims of the '235 patent.

60. Defendants' commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to the infringement of the '235 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 218956, Defendants will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '235 patent.

61. Defendants had actual knowledge of the ’235 patent prior to submitting Defendants’ ANDA and were aware that the submission of Defendants’ ANDA with the request for FDA approval prior to the expiration of the ’235 patent would constitute an act of infringement of the ’235 patent. Defendants had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not directly infringe, contribute to the infringement of, and/or induce the infringement of the ’235 patent.

62. In addition, Defendants submitted Defendants’ ANDA without adequate justification for asserting the ’235 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Defendants’ conduct in certifying invalidity, unenforceability, and/or noninfringement with respect to the ’235 patent thus renders this case “exceptional” under 35 U.S.C. § 285.

63. Boehringer will be irreparably harmed if Defendants are not enjoined from infringing and from actively inducing or contributing to the infringement of the ’235 patent. Boehringer does not have an adequate remedy at law and, considering the balance of hardships between Boehringer and Defendants, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT IV
INFRINGEMENT OF THE ’3,341 PATENT

64. Boehringer incorporates by reference paragraphs 1–63 as if fully set forth herein.

65. On information and belief, Defendants have submitted or caused the submission of Defendants’ ANDA to FDA and continue to seek FDA approval of Defendants’ ANDA.

66. Defendants have infringed the ’3,341 patent under 35 U.S.C. § 271(e)(2)(A) by submitting Defendants’ ANDA with a Paragraph IV certification and seeking FDA approval of Defendants’ ANDA prior to the expiration of the ’3,341 patent.

67. On information and belief, if Defendants' ANDA is approved, Defendants and their affiliates will make, offer for sale, sell, import, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing one or more claims of the '3,341 patent.

68. Defendants' commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to the infringement of the '3,341 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 218956, Defendants will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '3,341 patent.

69. Defendants had actual knowledge of the '3,341 patent prior to submitting Defendants' ANDA and were aware that the submission of Defendants' ANDA with the request for FDA approval prior to the expiration of the '3,341 patent would constitute an act of infringement of the '3,341 patent. Defendants had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not directly infringe, contribute to the infringement of, and/or induce the infringement of the '3,341 patent.

70. In addition, Defendants submitted Defendants' ANDA without adequate justification for asserting the '3,341 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Defendants' conduct in certifying invalidity, unenforceability, and/or noninfringement with respect to the '3,341 patent thus renders this case "exceptional" under 35 U.S.C. § 285.

71. Boehringer will be irreparably harmed if Defendants are not enjoined from infringing and from actively inducing or contributing to the infringement of the '3,341 patent. Boehringer does not have an adequate remedy at law and, considering the balance of hardships between Boehringer and Defendants, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT V
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '6,341 PATENT

72. Boehringer incorporates by reference paragraphs 1–71 as if fully set forth herein.

73. Boehringer's claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

74. On information and belief, if Defendants' ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Defendants and their affiliates.

75. On information and belief, Defendants know that healthcare professionals or patients will use the ANDA Product in accordance with the labeling sought by Defendants' ANDA, and Defendants will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '6,341 patent under one or more of 35 U.S.C. §§ 271(a), (b), and (c).

76. On information and belief, Defendants' infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after FDA approves Defendants' ANDA. Any such conduct before the '6,341 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '6,341 patent under one or more of 35 U.S.C. §§ 271(a), (b), and (c).

77. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Boehringer and Defendants concerning liability for the infringement of the '6,341 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

78. Boehringer will be substantially and irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Boehringer has no adequate remedy at law.

79. This case is exceptional, and Boehringer is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

COUNT VI
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '967 PATENT

80. Boehringer incorporates by reference paragraphs 1–79 as if fully set forth herein.

81. Boehringer's claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

82. On information and belief, if Defendants' ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Defendants and their affiliates.

83. On information and belief, Defendants know that healthcare professionals or patients will use the ANDA Product in accordance with the labeling sought by Defendants' ANDA, and Defendants will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '967 patent under one or more of 35 U.S.C. §§ 271(a), (b), and (c).

84. On information and belief, Defendants' infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained

of herein will begin immediately after FDA approves Defendants' ANDA. Any such conduct before the '967 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '967 patent under one or more of 35 U.S.C. §§ 271(a), (b), and (c).

85. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Boehringer and Defendants concerning liability for the infringement of the '967 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

86. Boehringer will be substantially and irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Boehringer has no adequate remedy at law.

87. This case is exceptional, and Boehringer is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

COUNT VII
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '235 PATENT

88. Boehringer incorporates by reference paragraphs 1–87 as if fully set forth herein.

89. Boehringer's claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

90. On information and belief, if Defendants' ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Defendants and their affiliates.

91. On information and belief, Defendants know that healthcare professionals or patients will use the ANDA Product in accordance with the labeling sought by Defendants' ANDA, and Defendants will therefore contribute to the infringement of and/or induce the

infringement of one or more claims of the '235 patent under one or more of 35 U.S.C. §§ 271(a), (b), and (c).

92. On information and belief, Defendants' infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after FDA approves Defendants' ANDA. Any such conduct before the '235 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '235 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

93. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Boehringer and Defendants concerning liability for the infringement of the '235 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

94. Boehringer will be substantially and irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Boehringer has no adequate remedy at law.

95. This case is exceptional, and Boehringer is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

COUNT VIII
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '3,341 PATENT

96. Boehringer incorporates by reference paragraphs 1–95 as if fully set forth herein.

97. Boehringer's claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

98. On information and belief, if Defendants' ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Defendants and their affiliates.

99. On information and belief, Defendants know that healthcare professionals or patients will use the ANDA Product in accordance with the labeling sought by Defendants' ANDA, and Defendants will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '3,341 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

100. On information and belief, Defendants' infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after FDA approves Defendants' ANDA. Any such conduct before the '3,341 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '3,341 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

101. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Boehringer and Defendants concerning liability for the infringement of the '3,341 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

102. Boehringer will be substantially and irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Boehringer has no adequate remedy at law.

103. This case is exceptional, and Boehringer is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

Wherefore, Boehringer respectfully requests the following relief:

A. A judgment that Defendants have infringed one or more claims of the '6,341, '967, '235, and '3,341 patents under 35 U.S.C. § 271(e)(2)(A);

B. A declaratory judgment that, under one or more of 35 U.S.C. §§ 271(a), (b), and (c), Defendants' commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of the ANDA Product, or inducing or contributing to such conduct, would constitute infringement of one or more claims of the '6,341, '967, '235, and '3,341 patents;

C. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Defendants, their affiliates and subsidiaries, and all persons and entities acting in concert with Defendants, from commercially manufacturing, using, offering for sale, or selling or importing any product that infringes the '6,341, '967, '235, and '3,341 patents, including the ANDA Product described in ANDA No. 218956;

D. The entry of an order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any FDA approval of ANDA No. 218956 shall be no earlier than the expiration date of the '6,341, '967, '235, and '3,341 patents, or any later expiration of exclusivity for the '6,341, '967, '235, and '3,341 patents, including any extensions or regulatory exclusivities;

E. A declaration under 28 U.S.C. § 2201 that if Defendants, their officers, agents, servants, employees, licensees, representatives, and attorneys, and any other persons acting or attempting to act in active concert or participation with them or acting on their behalf, engage in the commercial manufacture, use, offer for sale, sale and/or importation of the product described in ANDA No. 218956, it will constitute an act of direct and/or indirect infringement of the'6,341, '967, '235, and '3,341 patents;

F. An award of damages or other relief, pursuant to 35 U.S.C. § 271(e)(4)(C), if Defendants engage in the commercial manufacture, use, offer for sale, sale, and/or importation of the ANDA Product, or any product that infringes the '6,341, '967, '235, and '3,341 patents, or induces or contributes to such conduct, prior to the expiration of the '6,341, '967, '235, and '3,341 patents, or any later expiration of exclusivity for the '6,341, '967, '235, and '3,341 patents, including any extensions or regulatory exclusivities;

G. The entry of a judgment declaring that Defendants' acts render this case an exceptional case and awarding Boehringer its attorneys' fees pursuant to 35 U.S.C. §§ 271(e)(4) and 285;

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

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

Dated: September 12, 2024

s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiffs Boehringer Ingelheim Pharmaceuticals, Inc. and Boehringer Ingelheim International GmbH

Of Counsel:

Christopher N. Sipes
R. Jason Fowler
Eric R. Sonnenschein
Sarahi Uribe
Justin W. Burnam
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street NW
Washington, DC 20001-4956
(202) 662-6000

CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 AND 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matter captioned *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Anobri Pharmaceuticals US, LLC, et al.*, Civil Action No. 2:23-cv-03530-CCC-LDW (consolidated), is related to the matter in controversy because the matter in controversy involves the same parties and the same patents, and because Defendants are seeking FDA approval to market generic versions of similar pharmaceutical products.

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

Dated: September 12, 2024

s/ Charles M. Lizza
Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiffs Boehringer Ingelheim Pharmaceuticals, Inc. and Boehringer Ingelheim International GmbH

Of Counsel:

Christopher N. Sipes
R. Jason Fowler
Eric R. Sonnenschein
Sarahi Uribe
Justin W. Burnam
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street NW
Washington, DC 20001-4956
(202) 662-6000

EXHIBIT A

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

STIOLTO® RESPIMAT® (tiotropium bromide and olodaterol inhalation spray), for oral inhalation use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
STIOLTO RESPIMAT is a combination of tiotropium, an anticholinergic and olodaterol, a long-acting $beta_2$-adrenergic agonist (LABA) indicated for the long-term, once-daily maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). (1.1)

Important limitations:
- STIOLTO RESPIMAT is NOT indicated to treat acute deterioration of COPD. (1.1)
- STIOLTO RESPIMAT is NOT indicated to treat asthma. (1.1)

----------DOSAGE AND ADMINISTRATION----------
- For oral inhalation only.
- Two inhalations of STIOLTO RESPIMAT once-daily at the same time of day. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Inhalation spray: Each actuation from the mouthpiece delivers 2.5 mcg tiotropium (equivalent to 3.124 mcg tiotropium bromide monohydrate), and 2.5 mcg olodaterol (equivalent to 2.736 mcg olodaterol hydrochloride). Two actuations equal one dose. (3)

----------CONTRAINDICATIONS----------
- Use of a LABA, including STIOLTO RESPIMAT, without an inhaled corticosteroid is contraindicated in patients with asthma. (4)
- Hypersensitivity to tiotropium, ipratropium, olodaterol, or any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------
- LABA as monotherapy (without an inhaled corticosteroid) for asthma increases the risk of serious asthma-related events. (5.1)
- Do not initiate STIOLTO RESPIMAT in acutely deteriorating COPD patients. (5.2)
- Do not use for relief of acute symptoms. Concomitant short-acting $beta_2$-agonists can be used as needed for acute relief. (5.2)
- Do not exceed the recommended dose. Excessive use of STIOLTO RESPIMAT, or use in conjunction with other medications containing LABA can result in clinically significant cardiovascular effects and may be fatal. (5.3)
- Immediate hypersensitivity reactions: Discontinue STIOLTO RESPIMAT at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, urticaria, rash, bronchospasm, or anaphylaxis, occur. (5.4)
- Life-threatening paradoxical bronchospasm can occur. Discontinue STIOLTO RESPIMAT immediately. (5.5)
- Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, or sensitivity to sympathomimetic drugs. (5.6, 5.7)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to consult a physician immediately if this occurs. (5.8)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to consult a physician immediately if this occurs. (5.9)
- Be alert to hypokalemia and hyperglycemia. (5.11)

----------ADVERSE REACTIONS----------
The most common adverse reactions (>3% incidence and more than an active control) were nasopharyngitis, cough, and back pain.

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Other adrenergic drugs may potentiate effect. Use with caution. (5.3, 7.1)
- Xanthine derivatives, steroids, diuretics, or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution. (7.2, 7.3)
- MAO inhibitors, tricyclic antidepressants, and drugs that prolong QTc interval may potentiate effect on cardiovascular system. Use with extreme caution. (7.4)
- Beta-blockers may decrease effectiveness. Use with caution and only when medically necessary. (7.5)
- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of STIOLTO RESPIMAT with other anticholinergic-containing drugs. (7.6)

----------USE IN SPECIFIC POPULATIONS----------
Patients with moderate to severe renal impairment should be monitored closely for potential anticholinergic side effects. (2, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of COPD

STIOLTO RESPIMAT is a combination of tiotropium and olodaterol indicated for long-term, once-daily maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use

- STIOLTO RESPIMAT is not indicated to treat acute deteriorations of COPD *[see Warnings and Precautions (5.2)]*.
- STIOLTO RESPIMAT is not indicated to treat asthma. The safety and effectiveness of STIOLTO RESPIMAT in asthma have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of STIOLTO RESPIMAT is two inhalations once-daily at the same time of the day. Do not use STIOLTO RESPIMAT more than two inhalations every 24 hours.

2.2 Administration Information

For oral inhalation only.

Prior to first use, the STIOLTO RESPIMAT cartridge is inserted into the STIOLTO RESPIMAT inhaler and the unit is primed. When using the unit for the first time, patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use. If not used for more than 3 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use *[see Patient Counseling Information (17)]*.

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given STIOLTO RESPIMAT should be monitored closely for anticholinergic effects *[see Warnings and Precautions (5.10), Use in Specific Populations (8.5, 8.6, 8.7), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Spray: STIOLTO RESPIMAT consists of a STIOLTO RESPIMAT inhaler and an aluminum cylinder (STIOLTO RESPIMAT cartridge) containing a combination of tiotropium bromide (as the monohydrate) and olodaterol (as the hydrochloride). The STIOLTO RESPIMAT cartridge is intended only for use with the STIOLTO RESPIMAT inhaler.

Each actuation from the STIOLTO RESPIMAT inhaler delivers 2.5 mcg tiotropium (equivalent to 3.124 mcg tiotropium bromide monohydrate) and 2.5 mcg olodaterol (equivalent to 2.736 mcg olodaterol hydrochloride) from the mouthpiece.

Two actuations equal one dose.

4 CONTRAINDICATIONS

Use of a LABA, including STIOLTO RESPIMAT, without an inhaled corticosteroid is contraindicated in patients with asthma *[see Warnings and Precautions (5.1)]*. STIOLTO RESPIMAT is not indicated for the treatment of asthma.

STIOLTO RESPIMAT is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, olodaterol, or any component of this product *[see Warnings and Precautions (5.4)]*.

In clinical trials and postmarketing experience with tiotropium, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported. Hypersensitivity reactions were also reported in clinical trials with STIOLTO RESPIMAT.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

- The safety and efficacy of STIOLTO RESPIMAT in patients with asthma have not been established. STIOLTO RESPIMAT is not indicated for the treatment of asthma *[see Contraindications (4)]*.
- Use of long-acting $beta_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroids (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.
- A 28-week, placebo-controlled US study comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABA, including olodaterol, one of the active ingredients in STIOLTO RESPIMAT.
- No study adequate to determine whether the rate of asthma-related death is increased in patients treated with STIOLTO RESPIMAT has been conducted.
- Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

5.2 Deterioration of Disease and Acute Episodes

STIOLTO RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. STIOLTO RESPIMAT has not been studied in patients with acutely deteriorating COPD. The use of STIOLTO RESPIMAT in this setting is inappropriate.

STIOLTO RESPIMAT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. STIOLTO RESPIMAT has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist.

When beginning STIOLTO RESPIMAT, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing STIOLTO RESPIMAT, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If STIOLTO RESPIMAT no longer controls symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of STIOLTO RESPIMAT beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of STIOLTO RESPIMAT and Use With Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, STIOLTO RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta$_2$-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.4 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of STIOLTO RESPIMAT. If such a reaction occurs, therapy with STIOLTO RESPIMAT should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to STIOLTO RESPIMAT.

5.5 Paradoxical Bronchospasm

As with other inhaled medicines, STIOLTO RESPIMAT may cause paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, STIOLTO RESPIMAT should be stopped immediately and alternative therapy instituted.

5.6 Cardiovascular Effects

Olodaterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and/or symptoms. If such effects occur, STIOLTO RESPIMAT may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Long acting beta$_2$-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension.

5.7 Coexisting Conditions

Olodaterol, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

5.8 Worsening of Narrow-Angle Glaucoma

STIOLTO RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.9 Worsening of Urinary Retention

STIOLTO RESPIMAT should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.10 Renal Impairment

Because tiotropium is a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with STIOLTO RESPIMAT should be monitored closely for anticholinergic side effects *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

5.11 Hypokalemia and Hyperglycemia

Beta-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2)]*. The decrease in serum potassium is usually transient, not requiring supplementation. Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose.

In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment *[see Drug Interactions (7.2)]*, which may increase the susceptibility for cardiac arrhythmias.

Clinically notable decreases in serum potassium or changes in blood glucose were infrequent during clinical studies with long-term administration of olodaterol with the rates similar to those for placebo controls. Olodaterol has not been investigated in patients whose diabetes mellitus is not well controlled.

6 ADVERSE REACTIONS

LABA, such as olodaterol, one of the active components in STIOLTO RESPIMAT, as monotherapy (without an inhaled corticosteroid) for asthma, increase the risk of asthma-related events. STIOLTO RESPIMAT is not indicated for the treatment of asthma *[see Warning and Precautions (5.1)]*.

The following adverse reactions are described, or described in greater detail, in other sections:

- Immediate hypersensitivity reactions *[see Warnings and Precautions (5.4)]*
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.8)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice.

The clinical program for STIOLTO RESPIMAT included 7151 subjects with COPD in two 52-week active-controlled trials, one 12-week placebo-controlled trial, three 6-week placebo-controlled cross-over trials, and four additional trials of shorter duration. A total of 1988 subjects received at least 1 dose of STIOLTO RESPIMAT. Adverse reactions observed in the ≤12-week trials were consistent with those observed in the 52-week trials, which formed the primary safety database.

The primary safety database consisted of pooled data from the two 52-week double-blind, active-controlled, parallel group confirmatory clinical trials (Trials 1 and 2). These trials included 5162 adult COPD patients (72.9% males and 27.1% females) 40 years of age and older. Of these patients, 1029 were treated with STIOLTO RESPIMAT once daily. The STIOLTO RESPIMAT group was composed of mostly Caucasians (71.1%) with a mean age of 63.8 years and a mean percent predicted FEV_1 at baseline of 43.2%. In these two trials, tiotropium 5 mcg and olodaterol 5 mcg were included as active control arms and no placebo was used.

In these two clinical trials, 74% of patients exposed to STIOLTO RESPIMAT reported an adverse reaction compared to 76.6% and 73.3% in the olodaterol 5 mcg and tiotropium 5 mcg groups, respectively. The proportion of patients who discontinued due to an adverse reaction was 7.4% for STIOLTO RESPIMAT treated patients compared to 9.9% and 9.0% for olodaterol 5 mcg and tiotropium 5 mcg treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD.

The most common serious adverse reactions were COPD exacerbation and pneumonia.

Table 1 shows all adverse drug reactions that occurred with an incidence of >3% in the STIOLTO RESPIMAT treatment group and a higher incidence rate than the active comparator groups listed.

Table 1 Number and frequency of adverse drug reactions greater than 3% (and higher than any of the comparators tiotropium and/or olodaterol) in COPD patients exposed to STIOLTO RESPIMAT: Pooled data from the two 52-week, double-blind, active-controlled clinical trials in COPD patients 40 years of age and older

Treatment	**STIOLTO RESPIMAT (once daily)**	**Tiotropium (5 mcg once daily)**	**Olodaterol (5 mcg once daily)**
Body system (adverse drug reaction)	**n=1029 n (%)**	**n=1033 n (%)**	**n=1038 n (%)**
Infections and infestations			
Nasopharyngitis	128 (12.4)	121 (11.7)	131 (12.6)
Respiratory, thoracic, and mediastinal disorders			
Cough	40 (3.9)	45 (4.4)	31 (3.0)
Musculoskeletal and connective tissue disorders			
Back Pain	37 (3.6)	19 (1.8)	35 (3.4)

Other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in ≤3% of patients in clinical studies are listed below:

Metabolism and nutrition disorders: dehydration
Nervous system disorders: dizziness, insomnia
Eye disorders: glaucoma, intraocular pressure increased, vision blurred
Cardiac/vascular disorders: atrial fibrillation, palpitations, supraventricular tachycardia, tachycardia, hypertension
Respiratory, thoracic, and mediastinal disorders: epistaxis, pharyngitis, dysphonia, bronchospasm, laryngitis, sinusitis
Gastrointestinal disorders: dry mouth, constipation, oropharyngeal candidiasis, dysphagia, gastroesophageal reflux disease, gingivitis, glossitis, stomatitis, intestinal obstruction including ileus paralytic
Skin and subcutaneous disorders: rash, pruritus, angioneurotic edema, urticaria, skin infection, and skin ulcer, dry skin, hypersensitivity (including immediate reactions)
Musculoskeletal and connective tissue disorders: arthralgia, joint swelling
Renal and urinary disorders: urinary retention, dysuria, and urinary tract infection

COPD Exacerbation Reduction Trial
In a one year trial (Trial 5) of 7880 patients to compare rates of COPD exacerbations, 3939 patients were treated with STIOLTO RESPIMAT and 3941 patients were treated with tiotropium 5 mcg inhalation spray. The safety profile of STIOLTO RESPIMAT was similar to that of tiotropium 5 mcg inhalation spray and consistent with that documented in the STIOLTO RESPIMAT primary safety database.

7 DRUG INTERACTIONS

7.1 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of olodaterol, one component of STIOLTO RESPIMAT, may be potentiated *[see Warnings and Precautions (5.3, 5.6, 5.10, 5.11)]*.

7.2 Sympathomimetics, Xanthine Derivatives, Steroids, or Diuretics

Tiotropium has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids, without increases in adverse reactions. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of olodaterol *[see Warnings and Precautions (5.11)]*.

7.3 Non-Potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of STIOLTO RESPIMAT with non-potassium sparing diuretics.

7.4 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

STIOLTO RESPIMAT, as with other drugs containing $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

7.5 Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and the olodaterol component of STIOLTO RESPIMAT may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore,

patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

7.6 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid co-administration of STIOLTO RESPIMAT with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.8, 5.9) and Adverse Reactions (6)]*.

7.7 Inhibitors of Cytochrome P450 and P-gp Efflux Transporter

In a drug interaction study using the strong dual CYP and P-gp inhibitor ketoconazole, a 1.7-fold increase of olodaterol maximum plasma concentrations and AUC was observed *[see Pharmacokinetics (12.3)]*. Olodaterol was evaluated in clinical trials for up to one year at doses up to twice the recommended therapeutic dose. No dose adjustment of STIOLTO RESPIMAT is necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled clinical studies with STIOLTO RESPIMAT or its individual components, tiotropium bromide and olodaterol, in pregnant women to inform of drug-associated risk of adverse pregnancy-related outcomes. Animal reproduction studies were conducted with the individual components of STIOLTO RESPIMAT, tiotropium bromide and olodaterol. There are clinical considerations with the use of STIOLTO RESPIMAT in pregnant women *[see Clinical Considerations]*. STIOLTO RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal reproduction studies, no structural abnormalities were observed when tiotropium was administered by inhalation to pregnant rats and rabbits during the period of organogenesis at doses 790 and 8 times, respectively, the maximum recommended human daily inhalation dose (MRHDID). Increased post-implantation loss was observed in rats and rabbits administered tiotropium at maternally toxic doses 430 times and 40 times the MRHDID, respectively *[see Data]*. Based on animal studies, olodaterol was not teratogenic when administered to pregnant rats or rabbits during organogenesis at inhalation doses of approximately 2731 or 1353 times the MRHDID (on an AUC basis), in rats or rabbits, respectively *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Labor and Delivery

There are no adequate and well-controlled human studies that have investigated the effects of STIOLTO RESPIMAT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of STIOLTO RESPIMAT during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Data

Animal Data

Animal reproduction studies with the combination of tiotropium and olodaterol are not available; however, studies are available with the individual components.

Tiotropium

In 2 separate embryo-fetal development studies, pregnant rats and rabbits received tiotropium during the period of organogenesis at doses up to approximately 790 and 8 times the MRHDID, respectively (on a mcg/m^2 basis at inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at tiotropium doses of approximately 40 times the MRHDID (on a mcg/m^2 basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at a tiotropium dose of approximately 430 times the MRHDID (on a mcg/m^2 basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the MRHDID, respectively (on a mcg/m^2 basis at inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively).

Olodaterol

Olodaterol was not teratogenic in rats at inhalation doses approximately 2731 times the MRHDID (on an AUC basis at a maternal inhalation dose of 1054 mcg/kg/day). No significant effects occurred in rabbits at inhalation doses approximately 1353 times the MRHDID in adults (on an AUC basis at a maternal inhalation dose of 974 mcg/kg/day). Placental transfer of olodaterol was observed in pregnant rats.

Olodaterol has been shown to be teratogenic in New Zealand rabbits at inhalation doses approximately 7130 times the MRHDID in adults (on an AUC basis at a maternal inhalation dose of 2489 mcg/kg/day). Olodaterol exhibited the following fetal toxicities: enlarged or small heart atria or ventricles, eye abnormalities, and split or distorted sternum.

8.2 Lactation

Risk Summary

There are no data on the presence of tiotropium or olodaterol in human milk, the effects on the breastfed infant, or the effects on milk production. Tiotropium, olodaterol, and/or their metabolites are present in the milk of lactating rats, however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STIOLTO RESPIMAT and any potential adverse effects on the breastfed child from STIOLTO RESPIMAT or from the underlying maternal condition.

Data

The distributions of tiotropium bromide or olodaterol into milk were investigated in separate studies after a single intravenous administration of 10 mg/kg or 0.4 µmol/kg, respectively, to lactating rats. Tiotropium, olodaterol, and/or their metabolites are present in the milk of lactating rats at concentrations above those in plasma.

8.4 Pediatric Use

COPD does not normally occur in children. The safety and effectiveness of STIOLTO RESPIMAT in the pediatric population has not been established.

8.5 Geriatric Use

Based on available data, no adjustment of STIOLTO RESPIMAT dosage in geriatric patients is warranted *[see Clinical Pharmacology (12.3)]*.

Of the 1029 patients who received STIOLTO RESPIMAT at the recommended dose once daily in the clinical studies from the pooled 1-year database, 525 (51.0%) were <65 years of age, 407 (39.6%) were 65 to <75, 96 (9.3%) were 75 to <85, and 1 (0.1%) was ≥85.

No overall differences in effectiveness were observed, and in the 1-year pooled data, the adverse drug reaction profiles were similar in the older population compared to the patient population overall.

8.6 Hepatic Impairment

No dose adjustment is needed in patients with mild and moderate hepatic impairment. A study in subjects with severe hepatic impairment was not performed *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dose adjustment is required for patients with renal impairment. However, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with STIOLTO RESPIMAT should be monitored closely for anticholinergic side effects *[see Dosage and Administration (2), Warnings and Precautions (5.10), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

STIOLTO RESPIMAT contains both tiotropium bromide and olodaterol; therefore, the risks associated with overdosage for the individual components described below apply to STIOLTO RESPIMAT.

Tiotropium

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium. Dry mouth/throat and dry nasal mucosa occurred in a dose-dependent [10-40 mcg daily] manner, were observed following 14-day dosing of up to 40 mcg tiotropium bromide inhalation solution in healthy subjects.

Olodaterol

The expected signs and symptoms with overdosage of olodaterol are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., myocardial ischemia, angina pectoris, hypertension or hypotension, tachycardia, arrhythmias, palpitations, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of olodaterol.

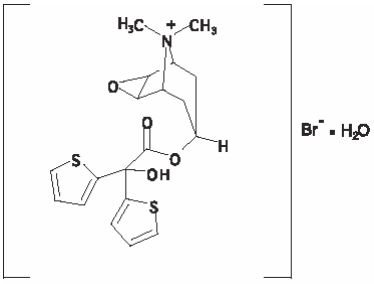
Treatment of overdosage consists of discontinuation of STIOLTO RESPIMAT together with institution of appropriate symptomatic and supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of STIOLTO RESPIMAT. Cardiac monitoring is recommended in cases of overdosage.

11 DESCRIPTION

STIOLTO RESPIMAT is a combination of tiotropium, an anticholinergic, and olodaterol, a long-acting beta$_2$-adrenergic agonist (LABA).

The drug substance tiotropium bromide monohydrate is chemically described as (1α, 2ß, 4ß, 5α, 7ß)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}] nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

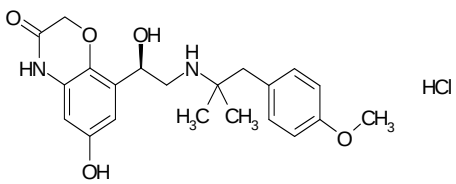
The structural formula is:



Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $C_{19}H_{22}NO_4S_2Br \bullet H_2O$.

The drug substance olodaterol hydrochloride is chemically described as 2H-1,4-Benzoxazin-3H(4H)-one, 6-hydroxy-8-[(1R)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethylethyl]-amino]ethyl]-, monohydrochloride. Olodaterol hydrochloride is a white to off-white powder that is sparingly-slightly soluble in water and slightly soluble in ethanol. The molecular weight is 422.9 g/mole (salt): 386.5 g/mole (base), and the molecular formula is $C_{21}H_{26}N_2O_5$ x HCl as a hydrochloride. The conversion factor from salt to free base is 1.094.

The structural formula is:



The drug product, STIOLTO RESPIMAT, is composed of a sterile aqueous solution of tiotropium bromide and olodaterol hydrochloride filled into a 4.5 mL plastic container crimped into an aluminum cylinder (STIOLTO RESPIMAT cartridge) for use with the STIOLTO RESPIMAT inhaler.

Excipients include water for injection, benzalkonium chloride, edetate disodium, and hydrochloric acid.

The STIOLTO RESPIMAT cartridge is only intended for use with the STIOLTO RESPIMAT inhaler. The STIOLTO RESPIMAT inhaler is a hand held, pocket sized oral inhalation device that uses mechanical energy to generate a slow-moving aerosol cloud of medication from a metered volume of the drug solution. The STIOLTO RESPIMAT inhaler has a light green-colored cap.

When used with the STIOLTO RESPIMAT inhaler each cartridge, containing 4 grams of sterile aqueous solution, delivers the labeled number of metered actuations after preparation for use. Each dose (one dose equals two actuations) from the STIOLTO RESPIMAT inhaler delivers 5 mcg tiotropium and 5 mcg olodaterol in 22.1 mcL from the mouthpiece. As with all inhaled drugs, the actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the inhaler and inspiration through the delivery system. The duration of inspiration should be at least as long as the spray duration (1.5 seconds).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

STIOLTO RESPIMAT

STIOLTO RESPIMAT contains both tiotropium and olodaterol. The properties described below for the individual components apply to STIOLTO RESPIMAT. These drugs represent 2 different classes of medication (an anticholinergic and a beta-agonist) that have different effects on clinical and physiological indices.

Tiotropium

Tiotropium is a long-acting, muscarinic antagonist which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

Olodaterol

Olodaterol is a long-acting $beta_2$-adrenergic agonist (LABA). The compound exerts its pharmacological effects by binding and activation of $beta_2$-adrenoceptors after topical administration by inhalation. Activation of these receptors in the airways results in a stimulation of intracellular adenyl cyclase, an enzyme that mediates the synthesis of cyclic-3', 5' adenosine monophosphate (cAMP). Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells. *In vitro* studies have shown that olodaterol has 241-fold greater agonist activity at $beta_2$-adrenoceptors compared to $beta_1$-adrenoceptors and 2299-fold greater agonist activity compared to $beta_3$-adrenoceptors. The clinical significance of these findings is unknown.

Beta-adrenoceptors are divided into three subtypes: $beta_1$-adrenoceptors predominantly expressed on cardiac muscle, $beta_2$-adrenoceptors predominantly expressed on airway smooth muscle, and $beta_3$-adrenoceptors predominantly expressed on adipose tissue. $Beta_2$-agonists cause bronchodilation. Although the $beta_2$-adrenoceptor is the predominant adrenergic receptor in the airway smooth muscle, it is also present on the surface of a variety of other cells, including lung epithelial and endothelial cells and in the heart. The precise function of $beta_2$-receptors in the heart is not known, but their presence raises the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

12.2 Pharmacodynamics

Cardiac Electrophysiology

STIOLTO RESPIMAT

In two 52-week randomized, double-blind trials using STIOLTO RESPIMAT that enrolled 5162 patients with COPD, ECG assessments were performed post-dose on days 1, 85, 169, and 365. In a pooled analysis the number of subjects with changes from baseline-corrected QT interval of >30 msec using both the Bazett (QTcB) and Fredericia (QTcF), corrections of QT for heart rate were not different for the STIOLTO RESPIMAT group compared to olodaterol 5 mcg and tiotropium 5 mcg across the assessments conducted.

Tiotropium

The effect of tiotropium dry powder for inhalation on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received tiotropium inhalation powder 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for tiotropium inhalation powder 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

In a multicenter, randomized, double-blind trial using tiotropium dry powder for inhalation that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30–60 msec was higher in the tiotropium group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical trials with tiotropium did not detect an effect of the drug on QTc intervals.

Olodaterol

The effect of olodaterol on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomized, placebo- and active (moxifloxacin)- controlled study at single doses of 10, 20, 30, and 50 mcg. Dose-dependent QtcI (individual subject corrected QT interval) prolongation was observed. The maximum mean (one-sided 95% upper confidence bound) difference in QTcI from placebo after baseline correction was 2.5 (5.6) ms, 6.1 (9.2) ms, 7.5 (10.7) ms, and 8.5 (11.6) ms following doses of 10, 20, 30, and 50 mcg, respectively.

The effect of 5 mcg and 10 mcg olodaterol on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 772 patients in the 48-week, placebo-controlled phase 3 trials. There were no dose- or time-related trends or patterns observed for the magnitudes of mean changes in heart rate or premature beats. Shifts from baseline to the end of treatment in premature beats did not indicate meaningful differences between olodaterol 5 mcg, 10 mcg, and placebo.

12.3 Pharmacokinetics

STIOLTO RESPIMAT

When STIOLTO RESPIMAT was administered by the inhalation route, the pharmacokinetic parameters for tiotropium and for olodaterol were similar to those observed when each active substance was administered separately.

Tiotropium

Tiotropium is administered as an inhalation spray. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Olodaterol
Olodaterol showed linear pharmacokinetics. On repeated once-daily inhalation, steady-state of olodaterol plasma concentrations was achieved after 8 days, and the extent of exposure was increased up to 1.8-fold as compared to a single dose.

Absorption
Tiotropium
Following inhalation of the solution by young healthy volunteers, urinary excretion data suggests that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Food is not expected to influence the absorption of tiotropium for the same reason. Maximum tiotropium plasma concentrations were observed 5 to 7 minutes after inhalation.

Olodaterol
Olodaterol reaches maximum plasma concentrations generally within 10 to 20 minutes following drug inhalation. In healthy volunteers the absolute bioavailability of olodaterol following inhalation was estimated to be approximately 30%, whereas the absolute bioavailability was below 1% when given as an oral solution. Thus, the systemic availability of olodaterol after inhalation is mainly determined by lung absorption, while any swallowed portion of the dose only negligibly contributes to systemic exposure.

Distribution
Tiotropium
The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier.

Olodaterol
Olodaterol exhibits multi-compartmental disposition kinetics after inhalation as well as after intravenous administration. The volume of distribution is high (1110 L), suggesting extensive distribution into tissue. *In vitro* binding of [^{14}C] olodaterol to human plasma proteins is independent of concentration and is approximately 60%.

Elimination
Metabolism
Tiotropium
The extent of metabolism is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, both not binding to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase 2 metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Olodaterol
Olodaterol is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety followed by conjugation. Of the six metabolites identified, only the unconjugated demethylation product binds to beta$_2$-receptors. This metabolite, however, is not detectable in plasma after chronic inhalation of the recommended therapeutic dose.

Cytochrome P450 isozymes CYP2C9 and CYP2C8, with negligible contribution of CYP3A4, are involved in the O-demethylation of olodaterol, while uridine diphosphate glycosyl transferase isoforms UGT2B7, UGT1A1, 1A7, and 1A9 were shown to be involved in the formation of olodaterol glucuronides.

Excretion
Tiotropium
The terminal half-life of tiotropium in COPD patients following once daily inhalation of 5 mcg tiotropium was approximately 25 hours. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). After inhalation of the solution by patients with COPD, urinary excretion is 18.6% (0.932 mcg) of the dose, the remainder being mainly non-absorbed drug in the gut that is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Olodaterol
Total clearance of olodaterol in healthy volunteers is 872 mL/min, and renal clearance is 173 mL/min. The terminal half-life following intravenous administration is 22 hours. The terminal half-life following inhalation in contrast is about 45 hours, indicating that the latter is determined by absorption rather than by elimination processes. However, the effective half-life at daily dose of 5 mcg calculated from C_{max} from COPD patients is 7.5 hours.

Following intravenous administration of [^{14}C]-labeled olodaterol, 38% of the radioactive dose was recovered in the urine and 53% was recovered in feces. The amount of unchanged olodaterol recovered in the urine after intravenous administration was 19%. Following oral administration, only 9% of olodaterol and/or its metabolites was recovered in urine, while the major portion was recovered in feces (84%). More than 90% of the dose was excreted within 6 and 5 days following intravenous and oral administration, respectively. Following inhalation, excretion of unchanged olodaterol in urine within the dosing interval in healthy volunteers at steady state accounted for 5% to 7% of the dose.

Drug Interactions
STIOLTO RESPIMAT
Pharmacokinetic drug interaction studies with STIOLTO RESPIMAT have not been performed; however, such studies have been conducted with individual components tiotropium and olodaterol.

When tiotropium and olodaterol were administered in combination by the inhaled route, the pharmacokinetic parameters for each component were similar to those observed when each active substance was administered separately.

Tiotropium
An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once-daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC_{0-4h}, a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of

tiotropium.

Common concomitant medications (long-acting beta$_2$-adrenergic agonists (LABA), inhaled corticosteroids (ICS)) used by patients with COPD were not found to alter the exposure to tiotropium.

Olodaterol
Drug-drug interaction studies were carried out using fluconazole as a model inhibitor of CYP 2C9 and ketoconazole as a potent P-gp (and CYP3A4, 2C8, 2C9) inhibitor.

Fluconazole: Co-administration of 400 mg fluconazole once a day for 14 days had no relevant effect on systemic exposure to olodaterol.
Ketoconazole: Co-administration of 400 mg ketoconazole once a day for 14 days increased olodaterol C_{max} by 66% and AUC_{0-1} by 68%.
Tiotropium: Co-administration of tiotropium bromide, delivered as a fixed-dose combination with olodaterol, for 21 days had no relevant effect on systemic exposure to olodaterol, and vice versa.

Specific Populations
Olodaterol
A pharmacokinetic meta-analysis showed that no dose adjustment is necessary based on the effect of age, gender, and weight on systemic exposure in COPD patients after inhalation of olodaterol.

Geriatric Patients
Tiotropium
As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (347 mL/min in COPD patients <65 years to 275 mL/min in COPD patients ≥65 years). This did not result in a corresponding increase in $AUC_{0-6,ss}$ and $C_{max,ss}$ values.

Renal Impairment
Tiotropium
Following inhaled administration of therapeutic doses of tiotropium to steady-state to patients with COPD, mild renal impairment (creatinine clearance 60 - <90 mL/min) resulted in 23% higher $AUC_{0-6,ss}$ and 17% higher $C_{max,ss}$ values. Moderate renal impairment (creatinine clearance 30 - <60 mL/min) resulted in 57% higher $AUC_{0-6,ss}$ and 31% higher $C_{max,ss}$ values compared to COPD patients with normal renal function (creatinine clearance ≥90 mL/min). In COPD patients with severe renal impairment (CLCR <30 mL/min), a single intravenous administration of tiotropium bromide resulted in 94% higher AUC_{0-4} and 52% higher C_{max} compared to COPD patients with normal renal function.

Olodaterol
Olodaterol levels were increased by approximately 40% in subjects with severe renal impairment. A study in subjects with mild and moderate renal impairment was not performed.

Hepatic Impairment
Tiotropium
The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

Olodaterol
Subjects with mild and moderate hepatic impairment showed no changes in C_{max} or AUC, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. A study in subjects with severe hepatic impairment was not performed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

STIOLTO RESPIMAT
No studies of the carcinogenicity, *in vitro* mutagenicity, or impairment of fertility were conducted with STIOLTO RESPIMAT, however, studies are available for the individual components, tiotropium and olodaterol.

Tiotropium
No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 59 mcg/kg/day, in an 83-week inhalation study in female mice at doses up to 145 mcg/kg/day, and in a 101-week inhalation study in male mice at doses up to 2 mcg/kg/day. These doses correspond to approximately 30, 40, and 0.5 times the recommended human daily inhalation dose (RHDID) on a mcg/m^2 basis, respectively.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assay in human lymphocytes *in vitro*, the mouse micronucleus assay *in vivo*, and the unscheduled DNA synthesis assay in primary rat hepatocytes *in vitro*.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 78 mcg/kg/day or greater (approximately 35 times the RHDID on a mcg/m^2 basis). No such effects were observed at 9 mcg/kg/day (approximately 4 times than the RHDID on a mcg/m^2 basis). The fertility index; however, was not affected at inhalation doses up to 1689 mg/kg/day (approximately 760 times the RHDID on a mcg/m^2 basis).

Olodaterol
Two-year inhalation studies were conducted in rats and mice to assess the carcinogenic potential of olodaterol. Lifetime treatment of female rats induced leiomyomas of the mesovarium at doses of 25.8 and 270 mcg/kg/day (approximately 18- and 198-fold, respectively, the RHDID on an AUC basis). No tumor findings were observed in male rats at doses up to 270 mcg/kg/day (approximately 230-fold the RHDID on an AUC basis). Lifetime treatment of female mice induced leiomyomas and leiomyosarcomas of the uterus at doses ≥76.9 mcg/kg/day (approximately 106-fold the RHDID on an AUC basis). No tumor findings were observed in male mice at doses up to 255 mcg/kg/day (approximately 455-fold the RHDID on an AUC basis). Increases in leiomyomas and leiomyosarcomas of the female rodent reproductive tract have been similarly demonstrated with other beta$_2$-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Olodaterol was not mutagenic in the *in vitro* Ames test or in the *in vitro* mouse lymphoma assay. Olodaterol produced increased frequency of micronuclei in rats after intravenous doses. The increased frequency of micronuclei was likely related to drug enhanced (compensatory) erythropoiesis. The mechanism for induction of micronuclei formation is likely not relevant at clinical exposures.

Olodaterol did not impair male or female fertility in rats at inhalation doses up to 3068 mcg/kg/day (approximately 2322 times the RHDID on an AUC basis).

14 CLINICAL STUDIES

The safety and efficacy of STIOLTO RESPIMAT were evaluated in a clinical development program that included three dose ranging trials, two active-controlled trials, three active- and placebo-controlled trials, and one placebo-controlled trial. The efficacy of STIOLTO RESPIMAT is based primarily on two 4-week dose-ranging trials in 592 COPD patients and two confirmatory active-controlled 52-week trials (Trials 1 and 2) in 5162 COPD patients.

Dose-Ranging Trials

Dose selection for STIOLTO RESPIMAT was primarily based on trials for the individual components, tiotropium bromide and olodaterol.

Dose selection was also supported by two randomized, double-blind, active-controlled, 4-week trials. In one trial in 232 patients with COPD, three tiotropium doses (1.25, 2.5, and 5 mcg) were given in combination with olodaterol 5 or 10 mcg and were evaluated compared to olodaterol monotherapy. Results demonstrated improvement in trough FEV_1 for the combination when compared to olodaterol alone. The difference in trough FEV_1 for the tiotropium bromide/olodaterol doses of 1.25/5, 2.5/5, and 5/5 mcg once daily from olodaterol 5 mcg were 0.054 L (95% CI 0.016, 0.092), 0.065 L (0.027, 0.103), and 0.084 L (0.046, 0.122), respectively. In the second trial in 360 patients with COPD, three olodaterol doses (2, 5, and 10 mcg) were given in combination with tiotropium 5 mcg and were evaluated compared to tiotropium monotherapy. The difference in trough FEV_1 for the tiotropium/olodaterol doses of 5/2, 5/5, and 5/10 mcg once daily from tiotropium 5 mcg were 0.024 L (95% CI -0.029, 0.076), 0.033 L (-0.019, 0.085), and 0.057 L (0.004, 0.110), respectively. Results of these trials supported the evaluation of once-daily doses of tiotropium bromide/olodaterol 2.5/5 mcg and 5/5 mcg in the confirmatory trials.

Confirmatory Trials

A total of 5162 COPD patients (1029 receiving STIOLTO RESPIMAT, 1038 receiving olodaterol 5 mcg, and 1033 receiving tiotropium bromide 5 mcg) were studied in two confirmatory trials of STIOLTO RESPIMAT. Trials 1 and 2 were 52-week, replicate, randomized, double-blind, active controlled, parallel group trials that compared STIOLTO RESPIMAT to tiotropium 5 mcg and olodaterol 5 mcg. In these trials, all products were administered via the RESPIMAT inhaler.

The trials enrolled patients 40 years of age or older with a clinical diagnosis of COPD, a smoking history of more than 10 pack-years, and moderate to very severe pulmonary impairment (post-bronchodilator FEV_1 less than 80% predicted normal [GOLD Stage 2-4]; post-bronchodilator FEV_1 to FVC ratio of less than 70%). All treatments were administered once daily in the morning. The primary endpoints were change from baseline in FEV_1 $AUC_{0\text{-}3hr}$ and trough FEV_1 after 24 weeks of treatment.

The majority of the 5162 patients were male (73%), white (71%) or Asian (25%), with a mean age of 64.0 years. Mean post-bronchodilator FEV_1 was 1.37 L (GOLD 2 [50%], GOLD 3 [39%], GOLD 4 [11%]). Mean $beta_2$-agonist responsiveness was 16.6% of baseline (0.171 L). Pulmonary medications allowed as concomitant therapy included inhaled steroids [47%] and xanthines [10%].

In both Trials 1 and 2, STIOLTO RESPIMAT demonstrated significant improvements in FEV_1 $AUC_{0\text{-}3hr}$ and trough FEV_1 after 24 weeks compared to tiotropium 5 mcg and olodaterol 5 mcg (Table 2). The increased bronchodilator effects of STIOLTO RESPIMAT compared to tiotropium 5 mcg and olodaterol 5 mcg were maintained throughout the 52-week treatment period. STIOLTO RESPIMAT displayed a mean increase in FEV_1 from baseline of 0.137 L (range: 0.133-0.140 L) within 5 minutes after the first dose. Patients treated with STIOLTO RESPIMAT used less rescue medication compared to patients treated with tiotropium 5 mcg and olodaterol 5 mcg.

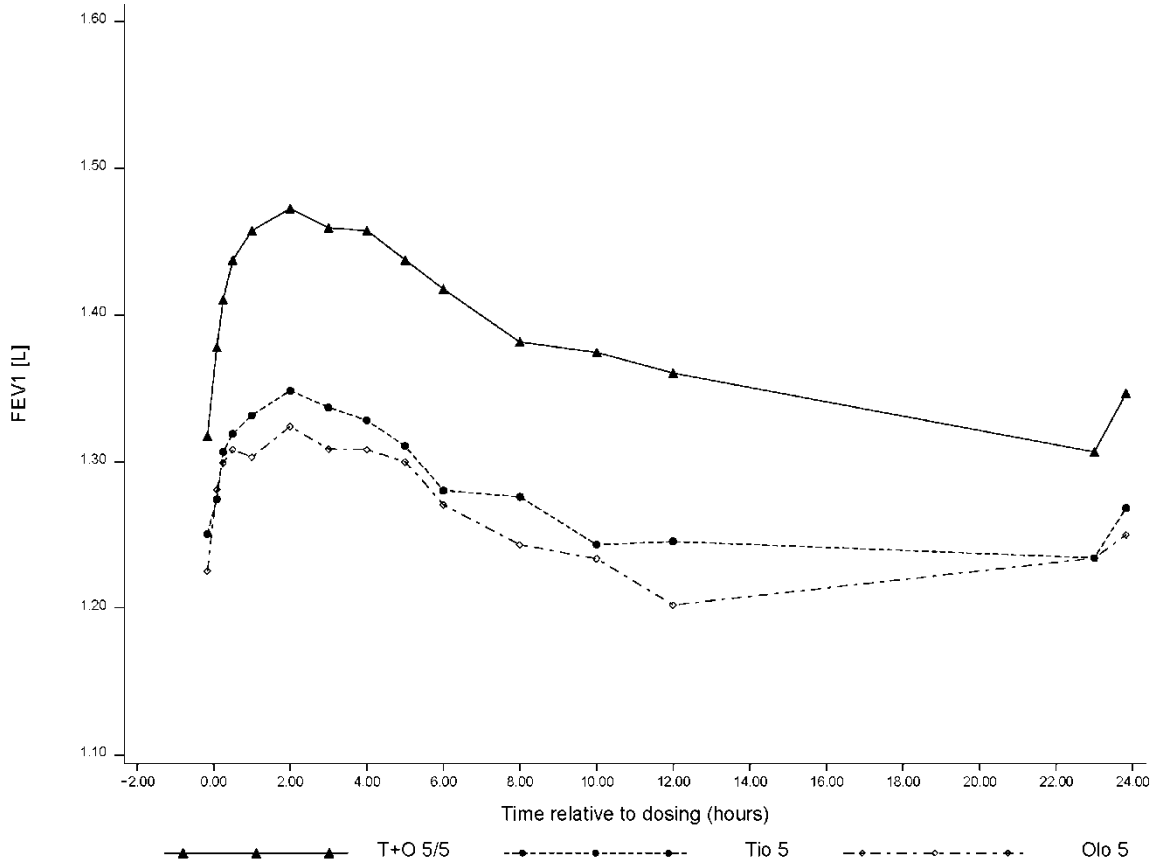
Table 2 FEV_1 $AUC_{0\text{-}3hr}$ and Trough FEV_1 response for STIOLTO RESPIMAT compared to tiotropium 5 mcg and olodaterol 5 mcg after 24 weeks (primary endpoints; Trials 1 and 2)

	Trial 1			Trial 2		
	n	**Mean (L)**	**Difference (L) (95% CI)**	**n**	**Mean (L)**	**Difference (L) (95% CI)**
FEV_1 $AUC_{0\text{-}3hr}$ response						
STIOLTO RESPIMAT	522	0.256	-	502	0.268	-
Tiotropium 5 mcg	526	0.139	0.117 (0.094, 0.140)	500	0.165	0.103 (0.078, 0.127)
Olodaterol 5 mcg	525	0.133	0.123 (0.100, 0.146)	507	0.136	0.132 (0.108, 0.157)
Trough FEV_1 response						
STIOLTO RESPIMAT	521	0.136	-	497	0.145	-
Tiotropium 5 mcg	520	0.065	0.071 (0.047, 0.094)	498	0.096	0.050 (0.024, 0.075)
Olodaterol 5 mcg	519	0.054	0.082 (0.059, 0.106)	503	0.057	0.088 (0.063, 0.113)

Pre-treatment baseline FEV_1: Trial 1=1.16 L; Trial 2=1.15 L
$p \leq 0.0001$ for all comparisons between STIOLTO RESPIMAT and the monotherapies.

For the subset of patients (n=521) who completed extended lung function measurements up to 12 hours post-dose, STIOLTO RESPIMAT showed a significantly greater FEV_1 response compared to tiotropium 5 mcg and olodaterol 5 mcg over the full 24-hour dosing interval. Results from Trial 2 are shown in Figure 1.

Figure 1 FEV_1 profile for STIOLTO RESPIMAT, tiotropium 5 mcg and olodaterol 5 mcg over a 24-hour dosing interval after 24 weeks (12 hr PFT subset from Trial 2)



The St. George's Respiratory Questionnaire (SGRQ) was assessed in Trials 1 and 2 and in two additional 12-week placebo-controlled trials (Trials 3 and 4).

In the first 12-week trial, SGRQ responder rates at week 12 (defined as an improvement in score of 4 or more as a threshold) were 53%, 42%, and 31% for STIOLTO RESPIMAT, tiotropium 5 mcg, and placebo, respectively, with odds ratios of 1.6 (95% CI 1.1, 2.4) and 2.5 (95% CI 1.6, 3.8) for STIOLTO RESPIMAT vs. tiotropium 5 mcg and STIOLTO RESPIMAT vs. placebo, respectively. In the second 12-week trial, results were similar with odds ratios of 1.5 (95% CI 1.0, 2.3) and 2.2 (95% CI 1.5, 3.4) for STIOLTO RESPIMAT vs. tiotropium 5 mcg and STIOLTO RESPIMAT vs. placebo, respectively. For the 52-week trials similar responder rates were seen. In Trial 1, the odds ratios for STIOLTO vs. tiotropium 5 mcg and STIOLTO vs. olodaterol 5 mcg at week 24 were 1.6 (95% CI 1.2, 2.0) and 1.9 (95% CI 1.5, 2.4), respectively. The results were similar in the 52-week Trial 2, with odds ratios for STIOLTO vs. tiotropium 5 mcg and STIOLTO vs. olodaterol 5 mcg of 1.3 (95% CI 1.0, 1.7) and 1.5 (95% CI 1.1, 1.9), respectively.

Exacerbations
Tiotropium 5 mcg Trials Evaluating Exacerbations
The effect of tiotropium 5 mcg inhalation spray on exacerbations was evaluated in three 48-week randomized, double-blind, placebo-controlled clinical trials that included COPD exacerbations as the primary endpoint. Exacerbations of COPD were defined as a complex of lower respiratory events/symptoms (increase or new onset) related to the underlying COPD, with duration of three days or more, requiring a prescription of antibiotics and/or systemic steroids and/or hospitalization. In a pooled analysis of the first two trials, tiotropium 5 mcg significantly reduced the number of COPD exacerbations compared to placebo with a rate ratio of 0.78 (95% CI 0.67, 0.92). In the third trial, tiotropium 5 mcg delayed the time to first COPD exacerbation compared to placebo with a hazard ratio of 0.69 (95% CI 0.63, 0.77).

STIOLTO RESPIMAT Trial Evaluating Exacerbations
In a one-year, randomized, double-blind, active-controlled parallel group clinical trial (Trial 5), the effect of STIOLTO RESPIMAT on COPD exacerbations was compared with tiotropium 5 mcg inhalation spray. Exacerbations were defined as above. Enrolled patients (3939 patients receiving STIOLTO RESPIMAT and 3941 patients receiving tiotropium 5 mcg inhalation spray) had a history of COPD exacerbation in the previous 12 months. The primary endpoint was the annualized rate of moderate to severe COPD exacerbations. The majority of patients were male (71%) and Caucasian (79%). The mean age was 66 years, and mean post-bronchodilator FEV_1 percent predicted was 45%. STIOLTO RESPIMAT treatment did not demonstrate superiority to tiotropium 5 mcg inhalation spray for the primary endpoint, the annualized rate of moderate to severe COPD exacerbations, with a rate ratio of 0.93 (99% CI, 0.85-1.02, p=0.0498). The study did not reach the pre-specified significance level of 0.01.

16 HOW SUPPLIED/STORAGE AND HANDLING

STIOLTO RESPIMAT Inhalation Spray is supplied in a labeled carton containing one STIOLTO RESPIMAT cartridge and one STIOLTO RESPIMAT inhaler.

The STIOLTO RESPIMAT cartridge is provided as an aluminum cylinder with a tamper protection seal on the cap. The STIOLTO RESPIMAT cartridge is only intended for use with the STIOLTO RESPIMAT inhaler and should not be interchanged with any other RESPIMAT device delivered product.

The STIOLTO RESPIMAT inhaler is a cylindrical shaped plastic inhalation device with a gray colored body and a clear base. The clear base is removed to insert the cartridge. The inhaler contains a dose indicator. The light green-colored cap and the written information on the label of the gray inhaler body indicate that it is labeled for use with the STIOLTO RESPIMAT cartridge.

STIOLTO RESPIMAT Inhalation Spray is available as:

- STIOLTO RESPIMAT Inhalation Spray: 60 metered actuations (NDC 0597-0155-61)
- STIOLTO RESPIMAT Inhalation Spray: 10 metered actuations (NDC 0597-0155-70) (institutional pack)

The STIOLTO RESPIMAT cartridge has a net fill weight of at least 4 grams and when used with the STIOLTO RESPIMAT inhaler, is designed to deliver the labeled number of metered actuations after preparation for use.

When the labeled number of actuations has been dispensed from the inhaler, the RESPIMAT locking mechanism will be engaged and no more actuations can be dispensed.

After assembly, the STIOLTO RESPIMAT inhaler should be discarded at the latest 3 months after first use or when the locking mechanism is engaged, whichever comes first.

Keep out of reach of children. Do not spray into eyes.

Storage
Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. Avoid freezing.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Serious Asthma-Related Events
Inform patients that LABA, such as STIOLTO RESPIMAT, when used as monotherapy [without an inhaled corticosteroid], increase the risk of serious asthma-related events, including asthma-related death. STIOLTO RESPIMAT is not indicated for the treatment of asthma.

Not for Acute Symptoms
STIOLTO RESPIMAT is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol. (The healthcare provider should provide the patient with such medication and instruct the patient in how it should be used.)

Instruct patients to notify their physician immediately if they experience any of the following:

- Worsening of symptoms
- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Instruct patients not to stop therapy with STIOLTO RESPIMAT without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists
Patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis should be instructed to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

When patients are prescribed STIOLTO RESPIMAT, other inhaled medications containing long-acting beta$_2$-agonists should not be used. Patients should not use more than the recommended once-daily dose of STIOLTO RESPIMAT. Excessive use of sympathomimetics may cause significant cardiovascular effects, and may be fatal.

Risks Associated with Beta$_2$-Agonist Therapy
Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Immediate Hypersensitivity Reactions
Inform patients that anaphylaxis, angioedema (including swelling of the lips, tongue, or throat), urticaria, rash, bronchospasm, or itching, may occur after administration of STIOLTO RESPIMAT. Advise patient to immediately discontinue treatment and consult a physician should any of these signs or symptoms develop.

Paradoxical Bronchospasm
Inform patients that STIOLTO RESPIMAT can produce paradoxical bronchospasm. Advise patients that if paradoxical bronchospasm occurs, patients should discontinue STIOLTO RESPIMAT.

Urinary Retention
Difficulty passing urine and dysuria may be symptoms of new or worsening prostatic hyperplasia or bladder outlet obstruction. Patients should be instructed to consult a physician immediately should any of these signs or symptoms develop.

Visual Effects
Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Inform patients to consult a physician immediately should any of these signs and symptoms develop. Advise patients that miotic eye drops alone are not considered to be effective treatment.

Inform patients that care must be taken not to allow the aerosol cloud to enter into the eyes as this may cause blurring of vision and pupil dilation.

Since dizziness and blurred vision may occur with the use of STIOLTO RESPIMAT, caution patients about engaging in activities such as driving a vehicle or operating appliances or machinery.

Instructions for Administering STIOLTO RESPIMAT
It is important for patients to understand how to correctly administer STIOLTO RESPIMAT inhalation spray using the STIOLTO RESPIMAT inhaler. Instruct patients that STIOLTO RESPIMAT inhalation spray should only be administered via the STIOLTO RESPIMAT inhaler and the STIOLTO RESPIMAT inhaler should not be used for administering other medications.

Instruct patients that priming STIOLTO RESPIMAT is essential to ensure appropriate content of the medication in each actuation.

When using the unit for the first time, the STIOLTO RESPIMAT cartridge is inserted into the STIOLTO RESPIMAT inhaler and the unit is primed. STIOLTO RESPIMAT patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then to repeat the process three more times. The unit is then considered primed and ready for use. If not used for more than 3 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

COL10537AK082021

PATIENT INFORMATION

STIOLTO® RESPIMAT® (sti-OL-to– RES peh mat)

(tiotropium bromide and olodaterol inhalation spray), for oral inhalation use

What is STIOLTO RESPIMAT?

- STIOLTO RESPIMAT combines an anticholinergic, tiotropium bromide and a long-acting beta$_2$-adrenergic agonist (LABA) medicine, olodaterol.
- Anticholinergic and LABA medicines such as STIOLTO RESPIMAT help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.
- STIOLTO RESPIMAT is a prescription medicine used to control the symptoms of COPD in adults with COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both.
- STIOLTO RESPIMAT is for long-term use and should be taken as 2 puffs 1 time each day, to improve the symptoms of COPD for better breathing.
- **STIOLTO RESPIMAT is not used to treat sudden symptoms of COPD.** Always have a beta$_2$-agonist inhaler medicine (rescue inhaler) with you to treat sudden symptoms of COPD. If you do not have a rescue inhaler, contact your healthcare provider to have one prescribed for you.
- **STIOLTO RESPIMAT is not for the treatment of asthma. It is not known if STIOLTO RESPIMAT is safe and effective in people with asthma.**
- **STIOLTO RESPIMAT should not be used in children. It is not known if STIOLTO RESPIMAT is safe and effective in children.**

Do not use STIOLTO RESPIMAT if you:

- have asthma.
- are allergic to tiotropium, ipratropium, olodaterol, or any of the ingredients in STIOLTO RESPIMAT. See the end of this Patient Information leaflet for a complete list of ingredients in STIOLTO RESPIMAT.

Before you use STIOLTO RESPIMAT, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- have eye problems, such as glaucoma. STIOLTO RESPIMAT can make your glaucoma worse.
- have prostate or bladder problems, or problems passing urine. STIOLTO RESPIMAT can make these problems worse.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if the medicines tiotropium or olodaterol in STIOLTO RESPIMAT can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if the medicines tiotropium or olodaterol in STIOLTO RESPIMAT passes into your breast milk and if it can harm your baby. You and your healthcare provider should decide if you will take STIOLTO RESPIMAT while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, eye drops, vitamins, and herbal supplements. STIOLTO RESPIMAT and certain other medicines may affect each other. This may cause serious side effects.

Especially tell your healthcare provider if you take:

- anticholinergics (including ipratropium, aclidinium, umeclidinium or another tiotropium-containing product such as SPIRIVA RESPIMAT or SPIRIVA HANDIHALER)
- atropine

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine.

How should I use STIOLTO RESPIMAT?

Read the step-by-step instructions for using STIOLTO RESPIMAT at the end of this Patient Information leaflet.

- **Do not** use STIOLTO RESPIMAT unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly. Ask your healthcare provider or pharmacist if you have any questions.
- STIOLTO RESPIMAT inhaler has a slow-moving mist that helps you inhale the medicine.
- Use STIOLTO RESPIMAT exactly as your healthcare provider tells you to use it. **Do not use STIOLTO RESPIMAT more often than prescribed**.
- **Use 1 dose (2 puffs) of STIOLTO RESPIMAT, 1 time each day, at the same time of the day.**
- If you miss a dose of STIOLTO RESPIMAT, take it as soon as you remember. Do not take more than 1 dose (2 puffs) in 24 hours.

- **If you take too much STIOLTO RESPIMAT, call your healthcare provider or go to the nearest hospital emergency room right away.**
- **Do not spray STIOLTO RESPIMAT in your eyes.** Your vision may become blurred and your pupils may become larger (dilated).
- STIOLTO RESPIMAT Inhalation Spray should only be given using the STIOLTO RESPIMAT inhaler. The STIOLTO RESPIMAT inhaler should not be used to give other medicines.
- Always use the new STIOLTO RESPIMAT inhaler that is provided with each new prescription.
- **STIOLTO RESPIMAT does not relieve sudden symptoms of COPD. You should not take extra doses of STIOLTO RESPIMAT to relieve sudden symptoms of COPD.** Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have a rescue inhaler medicine, call your healthcare provider to have one prescribed for you.
- If your COPD symptoms worsen over time, do not increase your dose of STIOLTO RESPIMAT, instead call your healthcare provider.
- **Do not** stop using STIOLTO RESPIMAT or other medicines to control or treat your COPD unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **Do not use STIOLTO RESPIMAT:**
  - more often than prescribed for you,
  - at a higher dose than prescribed for you, or
  - with other medicines that contain LABA or an anticholinergic for any reason. Ask your healthcare provider or pharmacist if any of your other medicines are LABA or anticholinergic medicines.
- **Call your healthcare provider or get emergency medical care right away if** your breathing problems worsen with STIOLTO RESPIMAT, you need to use your rescue inhaler medicine more often than usual, or your rescue inhaler medicine does not work as well for you at relieving your symptoms.

What are the possible side effects with STIOLTO RESPIMAT?
STIOLTO RESPIMAT can cause serious side effects, including:

- **serious problems from asthma.** People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines, such as olodaterol (one of the medicines in STIOLTO RESPIMAT), without also using a medicine called an inhaled corticosteroid, have an increased risk of serious problems from asthma, including being hospitalized, needing a tube placed in their airway to help them breathe, or death.
- **call your healthcare provider if breathing problems worsen over time while using STIOLTO RESPIMAT.** You may need a different treatment.
  Get emergency medical care if:
  - your breathing problems worsen quickly
  - you use your rescue inhaler medicine, but it does not relieve your breathing problems
- **using too much of a LABA medicine (one of the medicines in STIOLTO RESPIMAT) may cause**:
  - chest pain
  - fast and irregular heartbeat
  - tremor
  - increased blood pressure
  - headache
  - nervousness
- **COPD symptoms can get worse over time.** If your COPD symptoms worsen over time, do not increase your dose of STIOLTO RESPIMAT, instead call your healthcare provider.
- **serious allergic reactions including rash, hives, itching, swelling of the face, lips, tongue, throat, difficulties in breathing or swallowing**. Stop taking STIOLTO RESPIMAT and get emergency medical help right away if you get any symptoms of a serious allergic reaction after using STIOLTO RESPIMAT.
- **sudden shortness of breath can happen immediately after using STIOLTO RESPIMAT.** Sudden shortness of breath may be life-threatening. Stop taking STIOLTO RESPIMAT and call your healthcare provider or get emergency medical help right away if you get sudden shortness of breath after using STIOLTO RESPIMAT.
- **effects on your heart,** including fast or irregular heartbeat, palpitations, chest pain, and increased blood pressure.
- **new or worsening eye problems including acute narrow-angle glaucoma.** Symptoms of acute narrow-angle glaucoma include eye pain or discomfort, blurred vision, seeing halos or colored images around lights, and red eyes. Call your healthcare provider right away if you have any of these symptoms. Use caution as some of these eye problems can affect your ability to drive and operate appliances and machinery.
- **new or worsening urinary retention.** Symptoms of urinary retention may include difficulty urinating, painful urination, urinating frequently, or urinating in a weak stream or drips. Call your healthcare provider right away if you have any of these symptoms.
- **changes in laboratory blood levels including high blood sugar (hyperglycemia) and low levels of potassium (hypokalemia), which** may cause symptoms of muscle weakness or abnormal heart rhythm.

Common side effects of STIOLTO RESPIMAT include runny nose, cough, and back pain.

These are not all the side effects of STIOLTO RESPIMAT. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store STIOLTO RESPIMAT?

- Store STIOLTO RESPIMAT at room temperature, between 68°F to 77°F (20°C to 25°C).
- **Do not** freeze your STIOLTO cartridge or RESPIMAT inhaler.
- **Keep your STIOLTO RESPIMAT inhaler, cartridge, and all medicines out of the reach of children.**

General information about the safe and effective use of STIOLTO RESPIMAT

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use STIOLTO RESPIMAT for a condition for which it was not prescribed. Do not give STIOLTO RESPIMAT to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about STIOLTO RESPIMAT that is written for health professionals.

Active ingredients: Tiotropium bromide and olodaterol

Inactive ingredients: water for injection, benzalkonium chloride, edetate disodium, and hydrochloric acid

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

For more information about STIOLTO RESPIMAT, including current prescribing information, a video demonstration or a Quick Start Guide on how to use STIOLTO RESPIMAT, go to www.STIOLTO.com, scan the code, or call 1-800-542-6257.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 11/2021

Instructions for Use

STIOLTO® RESPIMAT® (sti-OL-to- RES peh mat)

(tiotropium bromide and olodaterol inhalation spray), for oral inhalation use

For Oral Inhalation Only

Do not spray STIOLTO RESPIMAT into your eyes.

Read these Instructions for Use before you start using STIOLTO RESPIMAT and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

You will need to use this inhaler 1 time each day, at the same time each day. Each time you use it take 2 puffs.

Do not turn the clear base before inserting the cartridge.

How to store your STIOLTO RESPIMAT inhaler

- Store STIOLTO RESPIMAT at room temperature between 68°F to 77°F (20°C to 25°C).
- **Do not** freeze your STIOLTO RESPIMAT cartridge and inhaler.
- If STIOLTO RESPIMAT has not been used for more than 3 days, release 1 puff towards the ground.
- If STIOLTO RESPIMAT has not been used for more than 21 days, repeat steps 4 to 6 under the “Prepare for first use” until a mist is visible. Then repeat steps 4 to 6 three more times.
- **Keep your STIOLTO RESPIMAT cartridge, inhaler, and all medicines out of the reach of children.**

How to care for your STIOLTO RESPIMAT inhaler

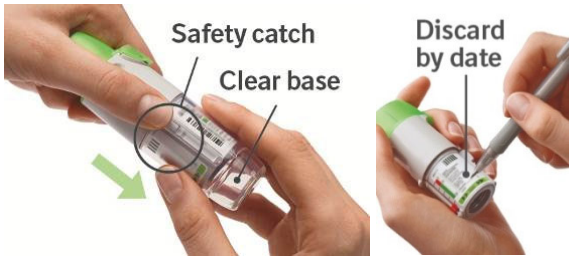
Clean the mouthpiece, including the metal part inside the mouthpiece, with a damp cloth or tissue only, at least 1 time each week. Any minor discoloration in the mouthpiece does not affect your STIOLTO RESPIMAT inhaler.

When to get a new STIOLTO RESPIMAT inhaler

- The scale on your inhaler will show the number of puffs you have, if used as indicated (2 puffs 1 time each day).
- The dose indicator will show you approximately how much medicine is left.
- When the dose indicator enters the red area of the scale, it will show you approximately how many puffs are left before you need a refill or new prescription.
- When the dose indicator reaches the end of the red scale, your STIOLTO RESPIMAT is empty and automatically locks. At this point, the clear base cannot be turned any further.

- Three months after insertion of cartridge, throw away the STIOLTO RESPIMAT even if it has not been used, or when the inhaler is locked, or when it expires, whichever comes first.

Prepare for first use

1. Remove clear base • Keep the cap closed. • Press the safety catch while firmly pulling off the clear base with your other hand. Be careful not to touch the piercing element. • Write the discard by date on the label (3 months from the date the cartridge is inserted).	
2. Insert cartridge • Insert the narrow end of the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it clicks into place.	
3. Replace clear base • Put the clear base back into place until it clicks. • Do not remove the clear base or the cartridge after it has been put together.	
4. Turn • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	
5. Open • Open the cap until it snaps fully open.	
6. Press • Point the inhaler toward the ground. • Press the dose-release button. • Close the cap. • If you do not see a mist, repeat steps 4 to 6 until a mist is seen. • After a mist is seen, repeat steps 4 to 6 three more times. • **After complete preparation of your inhaler, it will be ready to deliver the number of puffs on the label.**	

Daily use (T O P)

Turn • Keep the cap closed. • **Turn** the clear base in the direction of the arrows on the label until it clicks (half a turn).	
Open • **Open** the cap until it snaps fully open.	
Press • Breathe out slowly and fully. • Close your lips around the mouthpiece without covering the air vents. • Point the inhaler to the back of your throat. • While taking a slow, deep breath through your mouth, **Press** the dose-release button and continue to breathe in. • Hold your breath for 10 seconds or for as long as comfortable. • Repeat **Turn, Open, Press (TOP)** for a total of 2 puffs. • Close the cap until you use your inhaler again.	

Answers to Common Questions

It is difficult to insert the cartridge deep enough:
Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.

Did you insert the cartridge with the wide end first? Insert the cartridge with the narrow end first.

I cannot press the dose-release button:
Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).

Is the dose indicator on the STIOLTO RESPIMAT pointing to 0 (zero)? The STIOLTO RESPIMAT inhaler is locked after the labeled number of puffs have been used. Prepare and use your new STIOLTO RESPIMAT inhaler.

I cannot turn the clear base:
Did you turn the clear base already? If the clear base has already been turned, follow steps “Open” and “Press” under “Daily use” to get your medicine.

Is the dose indicator on the STIOLTO RESPIMAT pointing to 0 (zero)? The STIOLTO RESPIMAT inhaler is locked after the labeled number of puffs have been used. Prepare and use your new STIOLTO RESPIMAT inhaler.

The dose indicator on the STIOLTO RESPIMAT reaches 0 (zero) too soon:

Did you use STIOLTO RESPIMAT as indicated (2 puffs 1 time each day)? STIOLTO RESPIMAT will deliver the labeled number of puffs if used at 2 puffs 1 time each day.

Did you turn the clear base before you inserted the cartridge? The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not.

Did you spray in the air often to check whether the STIOLTO RESPIMAT is working? After you have prepared STIOLTO RESPIMAT, no test-spraying is required if used daily.

Did you insert the cartridge into a used STIOLTO RESPIMAT? Always insert a new cartridge into a **NEW** STIOLTO RESPIMAT.

My STIOLTO RESPIMAT sprays automatically:
Was the cap open when you turned the clear base? Close the cap, then turn the clear base.

Did you press the dose-release button when turning the clear base? Close the cap, so the dose-release button is covered, then turn the clear base.

Did you stop when turning the clear base before it clicked? Turn the clear base in a continuous movement until it clicks (half a turn).

My STIOLTO RESPIMAT does not spray:
Did you insert a cartridge? If not, insert a cartridge.

Did you repeat Turn, Open, Press (TOP) less than 3 times after inserting the cartridge? Repeat Turn, Open, Press (TOP) 3 times after inserting the cartridge as shown in steps 4 to 6 under “Prepare for first use”.

Is the dose indicator on the STIOLTO RESPIMAT pointing to 0 (zero)? You have used up all your medicine and the inhaler is locked.

For more information about STIOLTO RESPIMAT, including current prescribing information, a video demonstration or a Quick Start Guide on how to use STIOLTO RESPIMAT, go to www.STIOLTO.com, scan the code, or call 1-800-542-6257.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT 06877 USA

SPIRIVA®, HANDIHALER®, STIOLTO® and RESPIMAT® are registered trademarks of and are used under license from Boehringer Ingelheim International GmbH

Revised: November 2021

COL10537AK082021

EXHIBIT B

US007396341B2

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

(10) **Patent No.: US 7,396,341 B2**
(45) **Date of Patent: Jul. 8, 2008**

(54) **BLOCKING DEVICE FOR A LOCKING STRESSING MECHANISM HAVING A SPRING-ACTUATED OUTPUT DRIVE DEVICE**

(75) Inventors: **Michael Schyra**, Wuppertal (DE); **Herbert Wachtel**, Bingen (DE)

(73) Assignee: **Boehringer Ingelheim International GmbH**, Ingelheim (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1140 days.

(21) Appl. No.: **10/650,869**

(22) Filed: **Aug. 27, 2003**

(65) **Prior Publication Data**

US 2004/0094147 A1 May 20, 2004

Related U.S. Application Data

(60) Provisional application No. 60/458,212, filed on Mar. 27, 2003.

(30) **Foreign Application Priority Data**

Aug. 28, 2002 (DE) 102 39 443

(51) **Int. Cl.**
A61M 31/00 (2006.01)

(52) **U.S. Cl.** **604/92**; 128/203.15; 128/203.12; 604/82; 604/48

(58) **Field of Classification Search** 604/192, 604/92; 221/151, 265, 222, 237, 203, 204, 221/154, 152, 2, 6, 7; 70/278.7; 116/240, 116/241, 281, 288, 294, 319, 321, 324
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,263,475 A * 11/1993 Altermatt et al. 128/203.15
5,740,792 A * 4/1998 Ashley et al. 128/203.15
5,829,434 A * 11/1998 Ambrosio et al. 128/203.15

(Continued)

FOREIGN PATENT DOCUMENTS

WO WO 93 21980 A 11/1993

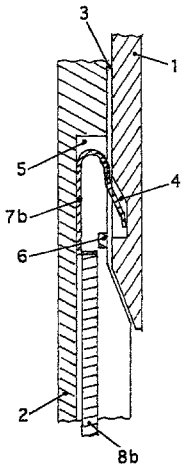
(Continued)

Primary Examiner—Terrell Mckinnon
Assistant Examiner—Ian K Holloway
(74) *Attorney, Agent, or Firm*—David A. Dow; Michael P. Morris; Mary-Ellen M. Devlin

(57) **ABSTRACT**

A locking-stressing-mechanism with spring-actuated output drive and a counter with which an apparatus of this kind is fitted, accommodated in a two part housing the two parts of which are mounted to be rotatable relative to each other, can be blocked by means of a pre-stressed leaf spring. The leaf spring is initially accommodated in a recess in the wall of one housing part. As soon as the permitted number of actuations has been reached a push rod pushes the leaf spring out of its resting position. The leaf spring then jumps into a recess in the wall of the other housing part and the two housing parts can no longer be rotated relative to each other. The push rod may be mounted on the pointer of the counter. This blocking device can only be overcome by the application of a force which is sufficient to destroy the device. The device is suitable for blocking a high pressure atomiser or a needleless injector with which a fluid is atomised to form an aerosol or a fluid is injected into a biological tissue.

11 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

5,871,007	A *	2/1999	Clark, Jr.	128/200.23
5,988,496	A *	11/1999	Bruna	235/91 R
6,065,471	A *	5/2000	Schaeffer et al.	128/203.15
6,453,795	B1 *	9/2002	Eicher et al.	92/23
6,729,330	B2 *	5/2004	Scarrott et al.	128/205.23
6,948,495	B2 *	9/2005	Seppala	128/203.15
2006/0285987	A1 *	12/2006	Jaeger et al.	417/572

FOREIGN PATENT DOCUMENTS

WO	WO 95 34874 A	12/1995
WO	WO 97 12687	4/1997
WO	WO 97 24586 A	7/1997

* cited by examiner

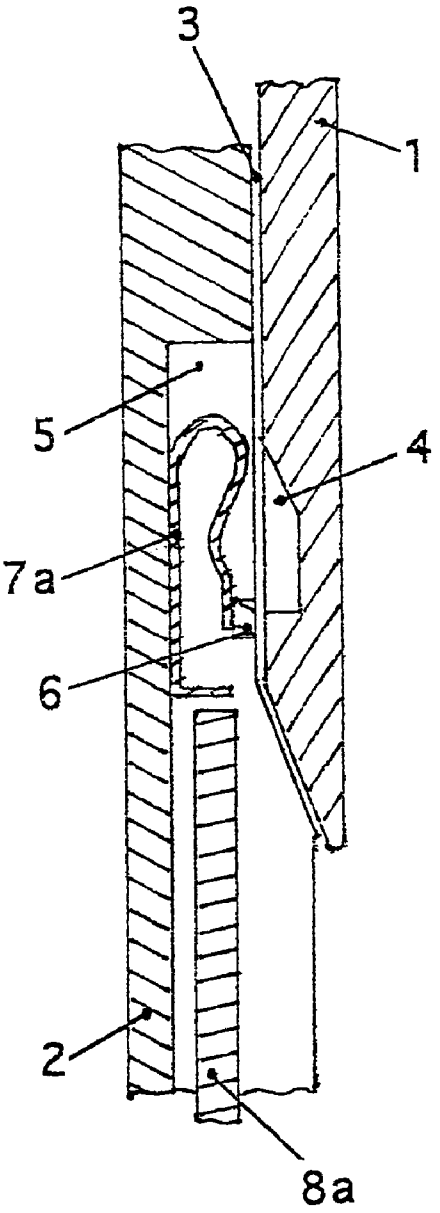


Fig. 1

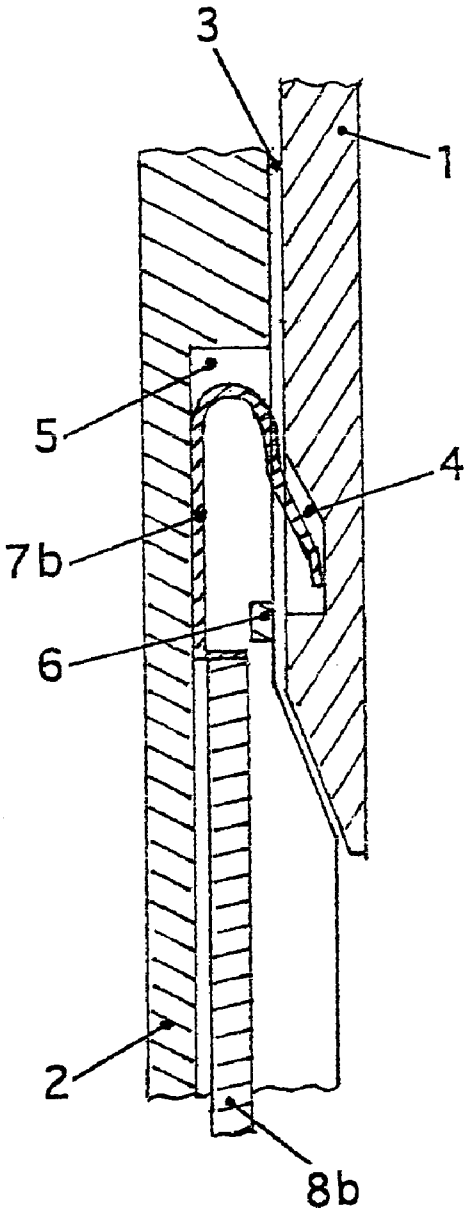


Fig. 2

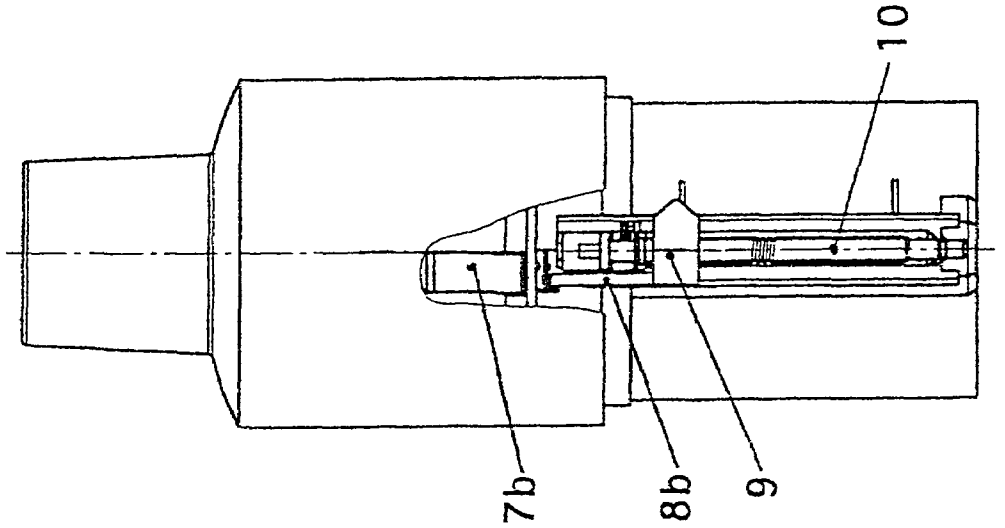


Fig. 4

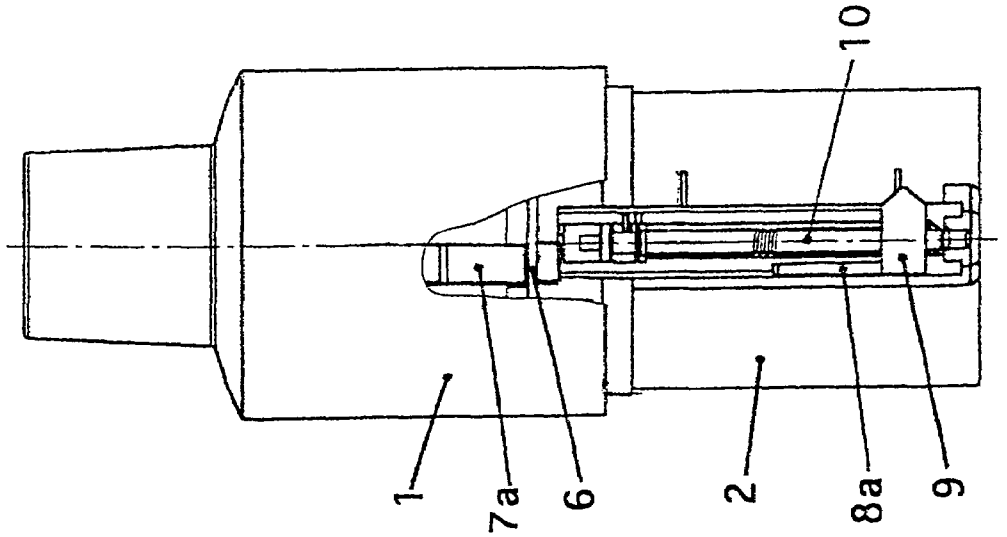


Fig. 3

BLOCKING DEVICE FOR A LOCKING STRESSING MECHANISM HAVING A SPRING-ACTUATED OUTPUT DRIVE DEVICE

The priority benefit of DE 10239443.1, filed Aug. 28, 2002 and U.S. Provisional Application No. 60/458,212, filed Mar. 27, 2003 are hereby claimed, both of which are incorporated by reference herein.

FIELD OF THE INVENTION

The invention relates to a blocking device by means of which the proper use of a device equipped with a locking-stressing mechanism and a spring-actuated output drive is prevented after a given number of actuations. The device may be, for example, a high pressure atomiser or a needleless injector.

BACKGROUND AND DESCRIPTION OF THE INVENTION

The aim of the invention is to reliably limit the period of use of such a device and meet safety requirements. The reasons for the limitation may be based on hygiene, medical or technical considerations.

The locking-stressing-mechanism, which is to be blocked after the permitted period of use has elapsed preferably comprises a helical thrust gear accommodated in a manually operated device, by means of which a rotary movement is converted into a linear movement and an operating spring is put under tension. The operating spring acts on a spring component of the locking-stressing-mechanism the movement of which is initially blocked as soon as the operating spring has reached the tensioned state. Secured in the spring component there may be a piston movably mounted in a cylinder. Inside the cylinder, in front of the piston, is a liquid which is expelled out through a nozzle as the locking mechanism of the locking-stressing mechanism is actuated by the piston driven by the operating spring. The number of actuations of the locking-stressing-mechanism and hence of the device can be counted by a mechanical counter.

WO-93/21980 describes a metered-dose inhaler. The dose of a substance to be inhaled is introduced, by means of a hand-operated device, from a supply of the substance contained in the inhaler, into a chamber from which the dose is expelled with the current of air which the user sucks in through the inhaler as they breathe in. The metered-dose inhaler is fitted with a counter which comprises a rotatable screw spindle and a rod, one end of which engages in the form of a nose in the thread of the screw spindle. The rod moves parallel to the screw spindle as the rotation of the spindle increases. The counter indicates, by means of the position of the nose-like end of the rod, the number of doses which have already been taken out of the supply of substance, or those which can still be taken out. The other end of the rod is movably held in a guide shaft into which the rod extends more deeply as the rotation of the screw spindle increases. As soon as the supply of substance in the inhaler is coming to an end, the nose-like end of the rod engaging in the screw spindle reaches that part of the spindle which has a number of courses of thread having a greater pitch than the rest of the screw spindle. As a result, on each rotation of the screw spindle, the rod moves along faster than before. The other end of the rod meanwhile bears on a flexible lever, and further actuation of the metered-dose inhaler is prevented.

WO-97/20590 describes a locking stressing mechanism for a spring-actuated output drive. WO-97/24586 describes a mechanical counter for a metering device. WO-97/12687 describes a device for generating high pressure in a fluid in a miniature arrangement provided with a locking stressing mechanism and a counter. The apparatus is used to atomise a fluid to produce an inhalable aerosol. WO-01/64268 describes a needleless injector which contains a locking stressing mechanism.

The pieces of equipment mentioned above by way of example are intended for repeated use, e.g. for repeated atomisation of a given amount of liquid to produce an aerosol for inhalation into the lungs, or for needleless injection of a given quantity of liquid underneath the skin of humans or animals. The quantity of liquid atomised or injected may contain a therapeutically active substance.

An object of the present invention is to provide a device for an apparatus which will reliably, effectively and finally prevent further use of the apparatus after a given number of actuations if there is a compelling reason for this. The apparatus comprises a locking-stressing-mechanism with an operating spring and a spring transfer member in which is accommodated a piston which is mounted to be movable in a cylinder. The components are housed in a two-part housing which comprises an upper housing part and a lower housing part. The two housing parts are mounted to be rotatable relative to each other. The operating spring is tensioned by means of a screw thrust gear by manually rotating the two housing parts relative to each other. At the same time as the housing parts are rotated relative to each other, a mechanical counter is actuated which comprises a threaded spindle and a slider. The threaded spindle is mounted in the wall of the lower housing part. The slider is moved up or down the spindle by an amount which depends on the number of rotations of the two housing parts relative to each other.

This problem is solved according to the invention by a device having the following characterising features:

- A recess is provided in the outer wall of the lower housing part and in the inner wall of the upper housing part. The two recesses are opposite each other when the two housing parts are in a given rotary position.
- In the recess in the lower housing part there is a movable blocking element which is located only in this recess before the blocking device is activated and allows the two housing parts to rotate relative to each other. After the activation of the blocking device the blocking element is located in both recesses and prevents the two housing parts from rotating relative to each other.
- By means of a push-rod which co-operates with the slider on the spindle of the counter, the blocking element is moved out of its resting position into the position which it occupies after activation of the blocking device.

On the one hand, the push-rod may be mounted on the slider to the side of the spindle of the counter. In this embodiment of the blocking device, during normal use of the device, the slider moves towards the upper spindle mounting and towards the upper housing part. The recess in the wall of the lower housing part is mounted next to the axis of the counter spindle. Before the slider makes contact with the upper spindle mounting, the push-rod moves the blocking element located in the recess in the wall of the lower housing part out of its resting position and thereby activates the blocking device.

The push-rod can also be constructed as an extension of the blocking element. In this embodiment, the end of the push-rod projects into the path travelled by the slider during normal use of the device before the slider comes to abut on the upper

mounting of the counter spindle. This embodiment works in exactly the same way as the embodiment described above.

In another embodiment of the blocking device the push rod may be constructed as an extension of the counter spindle and may project beyond the upper spindle mounting. In this case the counter spindle is mounted to be axially moveable. The recess in the wall of the lower housing part is preferably provided on the axis of the counter spindle. Before the blocking device is activated the counter spindle is pressed against the lower spindle mounting by a spring, e.g. a helical spring. In this embodiment of the blocking device the slider moves towards the lower spindle mounting during normal use of the device. As soon as the slider comes to abut on the lower spindle mounting, the counter spindle moves axially towards the upper housing part as it continues to rotate. The extension of the counter spindle in the form of a push rod moves the blocking element located in the recess in the wall of the lower housing part out of its resting position, thereby activating the blocking device.

In a reversal of the embodiments described, the blocking element may be pulled out of its resting position by the slider.

The blocking element located in the wall of the lower housing part may be axially or radially moveable. The blocking element may be a leaf spring, preferably a pre-stressed leaf spring with two legs preferably made of metal.

The blocking device according to the invention has the following advantages:

- It is suitable for miniaturised equipment.
- It is arranged between the housing parts which overlap one another and in its position of use in a device it is inaccessible to the user.
- It is easy to assemble.
- A blocking element in the form of a pre-stressed leaf spring with two legs is secured against movement in its resting position without any additional effort.
- A pre-stressed leaf spring can be pushed into or pulled out of its resting position with relatively little force.
- A pre-stressed leaf spring with two legs jumps abruptly from its resting position into the position it occupies when the blocking device is activated, as soon as it has been moved a certain distance by means of a push rod. Thus the response point of the blocking device is precisely fixed.
- The rotation of the two housing parts relative to one another is blocked directly as soon as the blocking element, which was originally located in the recess in the wall of the lower housing part, is situated in both recesses at the same time.
- The activated blocking device which contains a pre-stressed metal leaf spring can only be overcome by a force moment amounting to several Newton metres, which will destroy the blocked device.

The blocking device according to the invention is used for example in a high pressure atomiser or in a needleless injector. A medical liquid administered using such a device may contain a drug dissolved in a solvent. Suitable solvents include, for example, water, ethanol or mixture thereof. The drugs in question may be, for example, Berotec (fenoterol hydrobromide; 1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)-ethyl]-amino]-ethanol-hydrobromide), Atrovent (ipratropium bromide), Berodual (combination of fenoterol hydrobromide and ipratropium bromide), salbutamol (or albuterol), Combivent, Oxivent (oxitropium bromide), Ba 679 (tiotropium bromide), BEA 2108 (tropenol di-(2-thienyl glycolate), flunisolide, budesonide and others.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a partial longitudinal section through the wall of the lower and upper housing part of a blocking device in the resting position.

FIG. **2** shows a partial longitudinal section through the wall of an upper housing part of a blocking device in the active position.

FIG. **3** shows a longitudinal elevation of a blocking device cut open in the region of the counter of the blocking device in the resting position.

FIG. **4** shows a longitudinal elevation of a device cut open in the region of the counter of the blocking device in the active position.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A preferred embodiment of the blocking device according to the invention will be explained in more detail with reference to the figures. FIGS. **1** and **2** show partial longitudinal sections through the wall of the lower and upper housing part as well as a leaf spring as a blocking element and a push rod level with the recesses in the walls. The longitudinal section runs parallel to the axis of the lower and upper housing parts.

FIGS. **3** and **4** show a longitudinal elevation of a device cut open in the region of the counter and the blocking device.

In FIGS. **1** and **3** the blocking device is shown in the resting position. The blocking element is in its resting position and is located only in the recess in the wall of the lower housing part. FIGS. **2** and **4** show the blocking device activated. The blocking element has been moved out of its resting position and is located in both recesses in the walls of the two housing parts.

The upper housing part (**1**) overlaps the lower housing part (**2**). The gap (**3**) between the two housing parts, mounted to be rotatable relative to each other, is exaggerated in the drawing. In the upper housing part there is the recess (**4**) and in the lower housing part the recess (**5**). The recess (**5**) contains an undercut projection (**6**) which is connected to the lower housing part at the side walls of the recess (**5**). The push rod (**8***a*, **8***b*) projects into the recess in the wall of the lower housing part. The push rod is mounted on the slider (not shown in FIGS. **1** and **2**) which is located on the spindle (not shown in FIGS. **1** and **2**) of the counter. The blocking element is a leaf spring with two legs. In its resting position the leaf spring (**7***a*) is jammed between the base of the recess (**5**) and the undercut projection (**6**). The push rod (**8***a*) is shown in a position which it occupies shortly before making contact with the leaf spring (**7***a*). As the device is further actuated the push rod moves towards the leaf spring and pushes it out of its resting position, until the end of the leaf spring jumps forward behind the projection (**6**). If the two recesses (**4**) and (**5**) are not yet located opposite each other at this moment the end of the leaf spring which has jumped forward behind the projection (**6**) first makes contact with the inner wall of the upper housing part. As soon as the two recesses (**4**) and (**5**) are located opposite one another, as the rotation of the two housing parts relative to each other continues, the end of the leaf spring jumps into the recess (**4**). The leaf spring (**7***b*) is thus located in both recesses and the blocking device is activated.

FIG. **3** shows the spindle (**10**) of the counter on which the slider (**9**) is located in its (lower) starting position before the device is used for the first time. The push rod (**8***a*) is at some distance from the leaf spring (**7***a*).

In FIG. **4** the slider on the spindle is in its (top) end position in which it has made contact with the end of the leaf spring

(**8***b*) and pushed the leaf spring out of its resting position, as a result of which the blocking device has been activated.

The pre-stressed leaf spring (**7***a*; **7***b*) shown in the figures as a blocking element consists for example of spring steel about 0.2 mm thick and is about 3.5 mm wide. The two recesses in the walls of the two housing parts are about 4 mm wide and about 1 mm deep. Once the blocking device has been activated the two housing parts can only be rotated relative to one another by the application of considerable force (force moment about 3 Newton metres), but this destroys the device and makes it unusable.

What is claimed is:

1. Blocking device for an apparatus which comprises a locking-stressing-mechanism with an operating spring and a spring transfer member in which is accommodated a piston which is mounted to be moveable in a cylinder, and these components are housed in a two part housing which comprises an upper housing part and a lower housing part, said upper housing part having an inner wall and said lower housing part having an outer wall, and the two parts are mounted to be rotatable relative to each other, and said operating spring is tensioned by means of a screw thrust gear by manually rotating said two housing parts relative to each other, and at the same time as said housing parts are rotated relative to each other a mechanical counter is actuated which comprises a threaded spindle and a slider, and said threaded spindle is mounted in said wall of the lower housing part, and said slider is moved along said spindle by an amount which depends on the number of rotations of said two housing parts relative to each other, wherein a recess is provided in said outer wall of said lower housing part and in said inner wall of said upper housing part, and the two recesses are opposite each other when said two housing parts are in a given rotary position, and a moveable blocking element is provided which is located initially only in the recess in said lower housing part and a push rod for moving said blocking element partially into the recess in said upper housing part to prevent the upper and lower housing parts from rotating relative to each other is provided which cooperates with said slider on said spindle of said counter.

2. Blocking device according to claim **1**, wherein said push rod is mounted on the slider.

3. Blocking device according to claim **1**, wherein said push rod is mounted on the blocking element.

4. Blocking device according to claim **1**, wherein said push rod is constructed as an extension of the spindle of the counter and the spindle is mounted to be axially moveable.

5. Blocking device according to claim **1**, wherein said blocking element is moveable in the axial direction.

6. Blocking device according to claim **1**, wherein said blocking element is a pre-stressed leaf spring.

7. Blocking device according to claim **1**, wherein said blocking element is a pre-stressed leaf spring with two legs.

8. Blocking device according to claim **7**, wherein said pre-stressed leaf spring is further comprised of metal.

9. Use of a blocking device according to claim **1** for blocking an atomiser for atomising a liquid which contains a pharmaceutically active substance.

10. Use of the blocking device according to claim **1** for blocking a needleless injector for injecting a liquid which contains a pharmaceutical active substance into animal or human tissue.

11. A method for blocking a needleless injector for injecting a liquid which contains a pharmaceutically active substance into animal or human tissue, said method comprised of the use of a blocking device according to claim **1**.

* * * * *

EXHIBIT C

US009027967B2

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

(10) **Patent No.: US 9,027,967 B2**
(45) **Date of Patent: May 12, 2015**

(54) **DEVICE FOR CLAMPING A FLUIDIC COMPONENT**

(75) Inventors: **Johannes Geser**, Ingelheim (DE); **Matthias Hausmann**, Dortmund (DE)

(73) Assignee: **Boehringer Ingelheim International GmbH**, Ingelheim am Rhein (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 813 days.

(21) Appl. No.: **12/641,424**

(22) Filed: **Dec. 18, 2009**

(65) **Prior Publication Data**

US 2010/0154792 A1 Jun. 24, 2010

Related U.S. Application Data

(62) Division of application No. 11/031,171, filed on Jan. 7, 2005, now Pat. No. 7,837,235.

(30) **Foreign Application Priority Data**

Jan. 8, 2004 (DE) 10 2004 001 451

(51) **Int. Cl.**
B05B 1/00 (2006.01)

(52) **U.S. Cl.**
CPC ***B05B 1/00*** (2013.01)

(58) **Field of Classification Search**
USPC 285/249, 331, 332, 332.1–332.4, 334.1, 285/334.3, 382.4, 382.5
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,181,060	A	4/1916	Bennett
2,278,479	A	4/1942	Parker
2,331,020	A	10/1943	Frances
2,669,465	A	2/1954	Newell
3,249,372	A	5/1966	Pollack
3,747,960	A	7/1973	Bawa
3,757,960	A	9/1973	Hill et al.
3,997,111	A	12/1976	Thomas et al.
4,073,157	A	2/1978	Aylmer et al.
4,150,794	A	4/1979	Higgins
4,244,521	A	1/1981	Guse
4,313,570	A	2/1982	Olsen

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2291737	A1	12/1998
CA	2404360	A1	9/2001

(Continued)

OTHER PUBLICATIONS

Advisory Action for parent U.S. Appl. No. 11/031,171, filed Aug. 31, 2009.

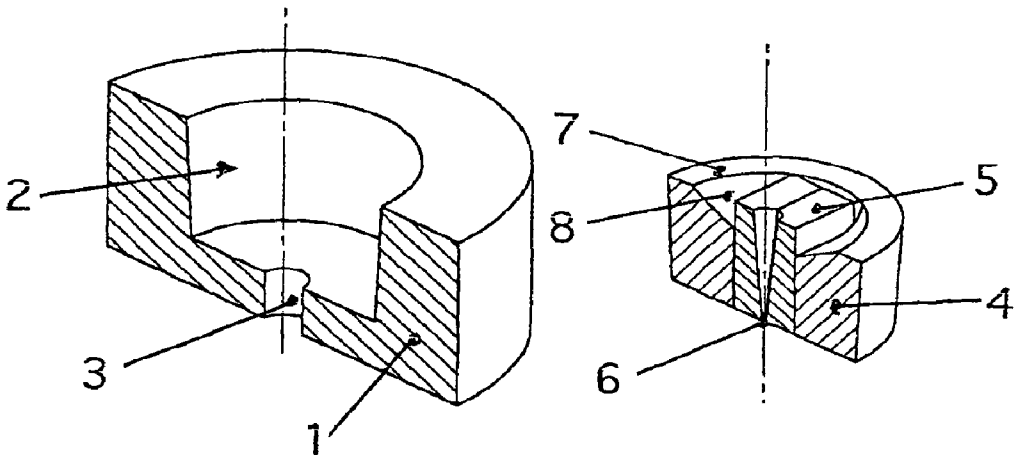
(Continued)

Primary Examiner — Aaron Dunwoody
Assistant Examiner — Fannie Kee
(74) *Attorney, Agent, or Firm* — Michael P. Morris; Mary-Ellen M. Devlin

(57) **ABSTRACT**

A fluidic component is arranged in an elastomeric shaped part the contour of which is matched to the outer contour of the component and to the inner contour of a holder. The elastomeric shaped part is chamfered towards the fluidic component on its pressure side. When the holder is assembled the elastomeric shaped part is deformed by a projection provided on a mating part and is put under uniformly distributed internal tension, after which the elastomeric shaped part surrounds the fluidic component to its full height.

11 Claims, 4 Drawing Sheets



(56) **References Cited**

U.S. PATENT DOCUMENTS

4,602,809	A *	7/1986	Ross et al.	285/50
4,660,773	A *	4/1987	O'Hanlon	239/596
4,936,512	A *	6/1990	Tremoulet, Jr.	239/596
5,033,681	A	7/1991	Munoz	
5,497,944	A	3/1996	Weston et al.	
5,716,082	A *	2/1998	Vogel et al.	285/343
5,848,753	A	12/1998	Wands et al.	
5,964,416	A	10/1999	Jaeger et al.	
6,176,442	B1	1/2001	Eicher et al.	
6,223,933	B1	5/2001	Hochrainer et al.	
6,481,435	B2	11/2002	Hochrainer et al.	
6,491,897	B1	12/2002	Freund et al.	
6,685,691	B1	2/2004	Freund et al.	
6,846,413	B1	1/2005	Kadel et al.	
6,977,042	B2	12/2005	Kadel et al.	
6,986,346	B2	1/2006	Hochrainer et al.	
7,040,311	B2	5/2006	Hochrainer et al.	
7,090,093	B2	8/2006	Hochrainer et al.	
7,314,187	B2	1/2008	Hochrainer et al.	
7,837,235	B2	11/2010	Geser et al.	
2001/0008632	A1	7/2001	Freund et al.	
2001/0032642	A1	10/2001	Bach et al.	
2002/0007155	A1	1/2002	Freund et al.	
2003/0064032	A1	4/2003	Lamche et al.	
2003/0066524	A1	4/2003	Hochrainer et al.	
2004/0010239	A1	1/2004	Hochrainer et al.	
2004/0143235	A1	7/2004	Freund et al.	
2004/0159319	A1	8/2004	Kadel et al.	
2004/0182867	A1	9/2004	Hochrainer et al.	
2005/0001076	A1	1/2005	Eicher et al.	
2005/0032494	A1	2/2005	Swant	
2005/0159441	A1	7/2005	Hochrainer et al.	
2005/0194472	A1	9/2005	Geser et al.	
2005/0263618	A1	12/2005	Spallek et al.	
2006/0196500	A1	9/2006	Hochrainer et al.	
2006/0239930	A1	10/2006	Lamche et al.	
2006/0258993	A1	11/2006	Hochrainer et al.	
2006/0285987	A1	12/2006	Jaeger et al.	
2009/0114215	A1	5/2009	Boeck et al.	
2009/0185983	A1	7/2009	Freund et al.	
2010/0154792	A1	6/2010	Geser et al.	

FOREIGN PATENT DOCUMENTS

CA	2653183	A1	12/2007
CA	2653422	A1	12/2007
DE	4115131	A1	11/1991
DE	19722338	A1	12/1998
EP	0046664	A1	3/1982
WO	9114468	A1	10/1991
WO	9407607	A1	4/1994
WO	9701329		1/1997
WO	9712683	A1	4/1997
WO	9712687	A1	4/1997
WO	9827959	A2	7/1998
WO	9916530	A1	4/1999
WO	0164268	A1	9/2001
WO	03002045	A1	1/2003
WO	2005065836	A1	7/2005
WO	2007141201	A1	12/2007
WO	2007141203	A1	12/2007

OTHER PUBLICATIONS

Office Action for parent U.S. Appl. No. 11/031,171, filed Jun. 1, 2009.

Office Action for parent U.S. Appl. No. 11/031,171, filed Aug. 19, 2008.

International Search Report for PCT/EP2004/014764 mailed Apr. 15, 2004.

* cited by examiner

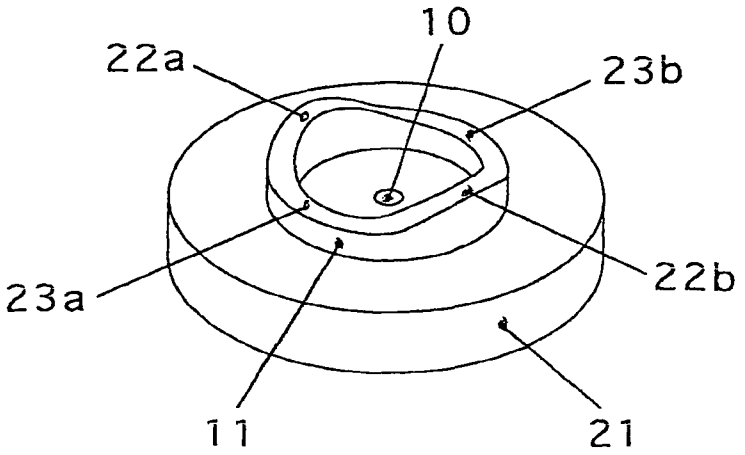


Fig. 2

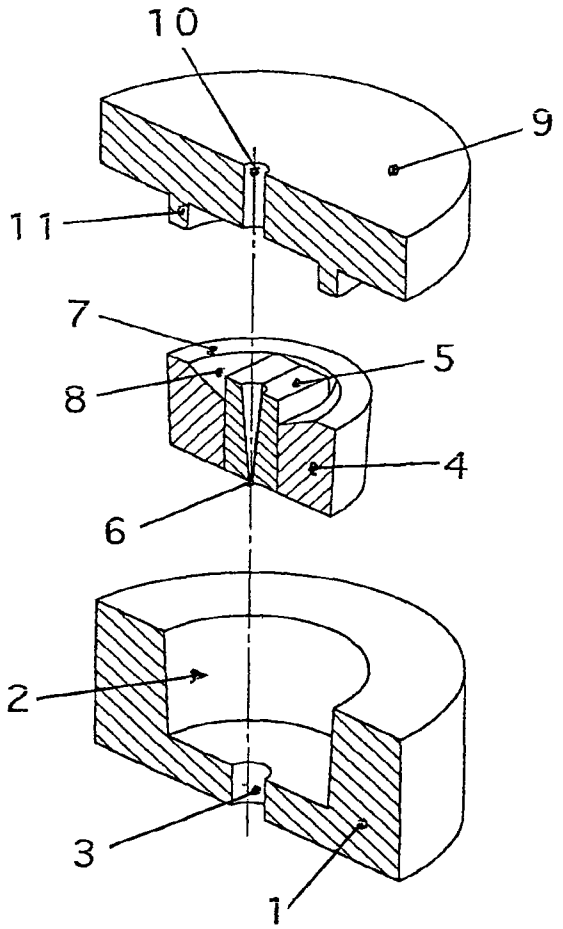


Fig. 1c

Fig. 1b

Fig. 1a

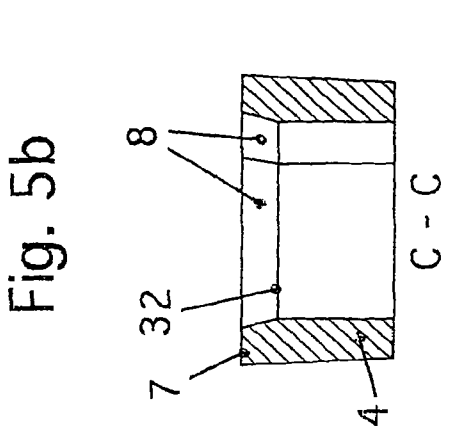


Fig. 5b

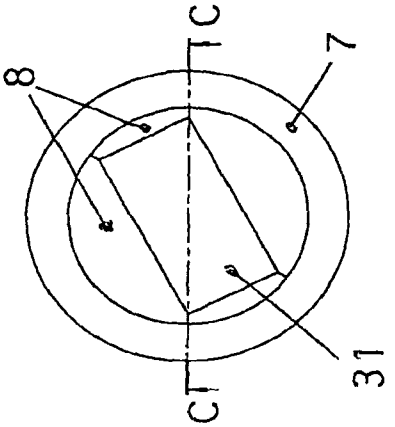


Fig. 5a

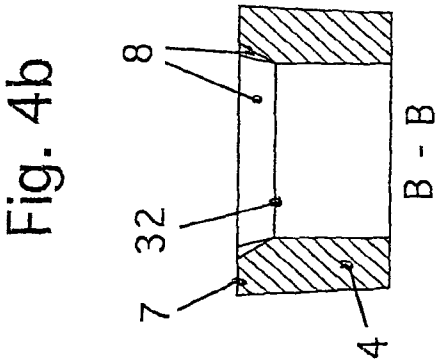


Fig. 4b

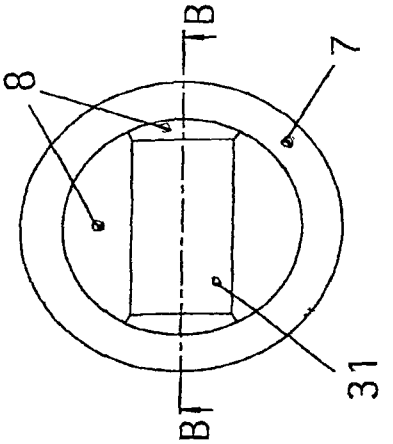


Fig. 4a

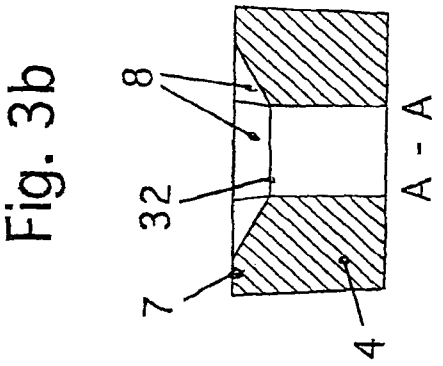


Fig. 3b

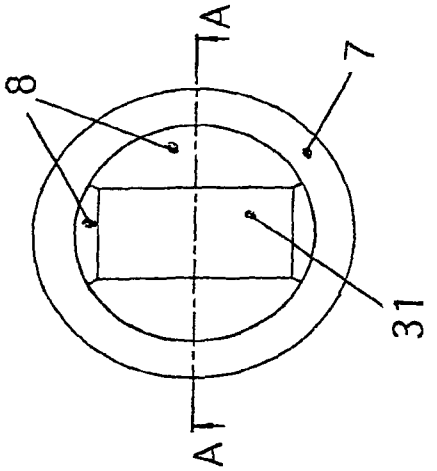
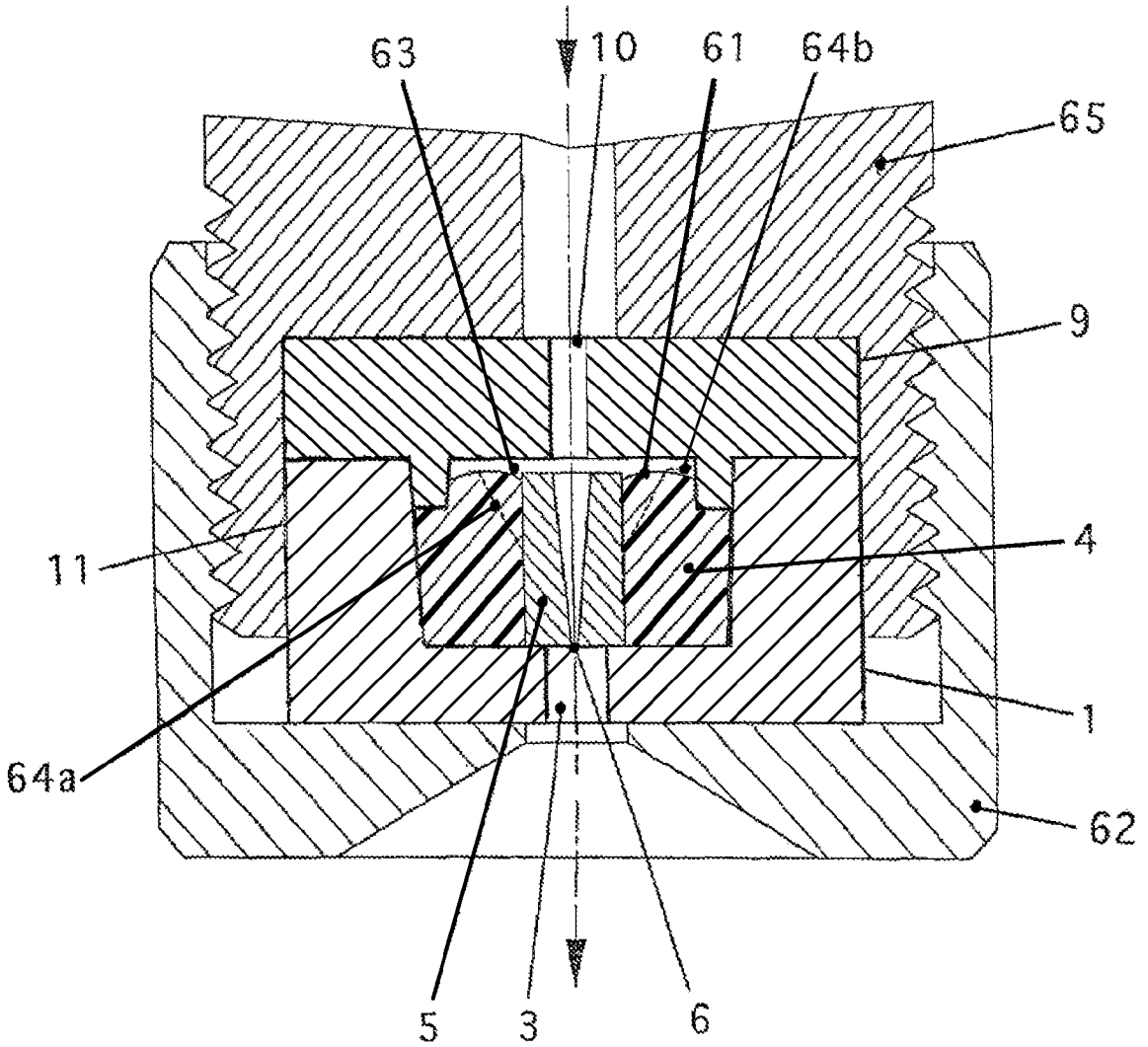


Fig. 3a

FIG. 6



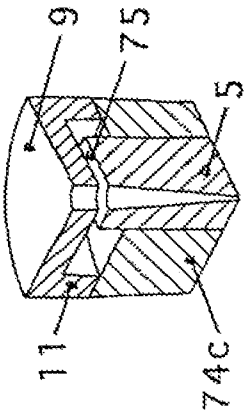


Fig. 8c
Prior Art

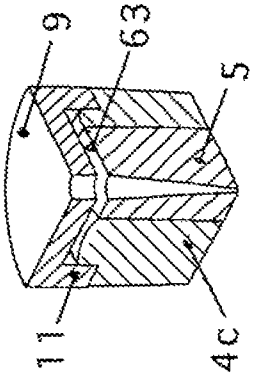


Fig. 7c

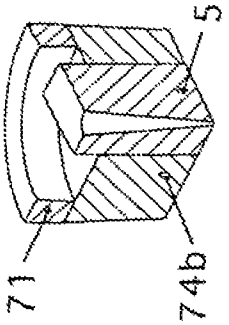


Fig. 8b
Prior Art

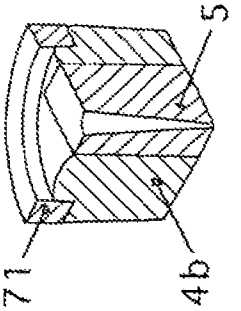


Fig. 7b

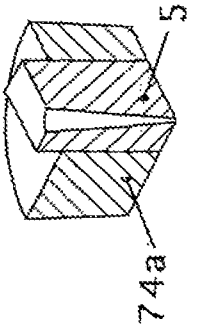


Fig. 8a
Prior Art

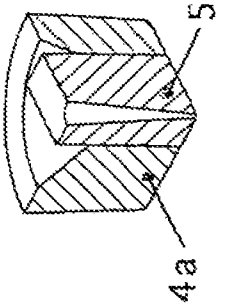


Fig. 7a

DEVICE FOR CLAMPING A FLUIDIC COMPONENT

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to a device for clamping a fluidic component, particularly a nozzle, particularly in the high pressure region. Of particular interest are holders for micro-engineered components, particularly micro-engineered nozzles which are to be produced by micro-engineering. Such nozzles are used for example in nebulizers for producing propellant-free medicinal aerosols used for inhalation.

The aim of the invention is to further improve the clamping of a fluidic component consisting of a wear-resistant, hard, and generally brittle material, and to increase the reliability of the holder.

2. Brief Description of the Prior Art

Micro-engineered nozzles having for example a nozzle aperture of less than 10 μm are described for example in WO 94/07607 and WO 99/16530. The inhalable droplets produced thereby have a mean diameter of about 5 μm, when the pressure of the liquid to be nebulized is from 5 MPa (50 bar) to 40 MPa (400 bar). The nozzles may for example be made from thin sheets of silicon and glass. The external dimensions of the nozzles are in the millimeter range. A typical nozzle consists for example of a cuboid with sides measuring 1.1 mm, 1.5 mm and 2.0 mm, made up of two sheets. Nebulizers for producing propellant-free aerosols in which the device according to the invention for clamping a fluidic component can be used are known from WO 91/14468 or WO 97/12687.

The term fluidic component denotes a component which is exposed to a pressurized fluid, and the pressure is also present inside the component, for example in a nozzle bore. Such a component may be kept pressure-tight for example by pressing into a holder of hard material if the material of the component can withstand mechanical forces without collapsing or deforming to an unacceptable degree. At high pressures, seals of deformable material, e.g. copper, or hard material which can be pressed in with great force are used. In the case of components made of brittle material the known processes for pressure-tight clamping of the component require considerable effort and great care. It is impossible to predict with any reliability the service life of a fluidic component clamped in this way.

U.S. Pat. No. 3,997,111 describes a fluid jet cutting device with which a high-speed fluid jet is produced which is used for cutting, drilling or machining material. The nozzle body is cylindrical and consists e.g. of sapphire or corundum. The setting ring is pressed into an annular recess in the nozzle carrier and seals off the nozzle body against the nozzle carrier.

U.S. Pat. No. 4,313,570 describes a nozzle holder for a water jet cutting device wherein the nozzle body is surrounded by a ring of elastomeric material which is in turn mounted in a recess in the holder. The recess is in the form of a straight cylinder. The cross-section of the ring is rectangular. The outer surface of the recess and the outer and inner surfaces of the ring are arranged concentrically to the axis of the nozzle body and run parallel to one another and to the axis of the nozzle body.

WO 97/12683 discloses a device for clamping a fluidic component which is subjected to fluid pressure, which is suitable for components consisting of a wear-resistant, hard and hence generally brittle material, and which does not produce any excessively great local material tensions in the component. The fluidic component is arranged in a holder which makes contact with the fluidic component on its low pressure side. The fluidic component is surrounded by an elastomeric shaped part the outer contour of which is adapted to the inner contour of the holder and the inner contour of which is adapted to the outer contour of the fluidic component. The elastomeric component surrounds the entire circumference of the fluidic component. At least one free surface of the elastomeric component is exposed to the pressurized fluid. The holder may have a projection on the inside underneath which the elastomeric shaped part is pushed. It has proved difficult to generate internal tension in the elastomeric shaped part which is sufficiently great, even at low fluid pressures, and which is spatially roughly uniformly distributed in the elastomeric shaped part.

This known device has proved pressure-tight when subjected substantially constantly to moderate and high fluid pressures. When subjected to alternating fluid pressures fluctuating between a high peak value and a very low value, the known device is in need of improvement for long-term use.

The problem thus arises of providing a device for clamping a fluidic component which is reliably leak-tight even when subjected to alternating loading from a sharply fluctuating fluid pressure in long-term use. The components needed should be cheap to manufacture and should also be capable of being assembled with relative ease.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1***a* is a cross-sectional, elevational view of a pot-shaped holder (**1**).

FIG. **1***b* is a cross-sectional, elevational view of an elastomeric shaped part (**4**) and a cuboid, fluidic component (**5**).

FIG. **1***c* is a cross-sectional, elevational view of a mating part (**9**) with a bore (**10**) and an annular projection (**11**).

FIG. **2** is an elevational view of the underside of the mating part (**9**).

FIGS. **3***a*, **4***a*, and **5***a* show the elastomeric shaped part viewed perpendicularly.

FIGS. **3***b*, **4***b*, and **5***b*, are cross-sections through the elastomeric shaped part.

FIG. **6** shows a cross section through the assembled holder which is mounted on a container for a fluid.

FIGS. **7***a*, **7***b* and **7***c* show the holder according to the invention in cross-hatched cross-section.

FIGS. **8***a*, **8***b*, and **8***c* show a prior-art embodiment.

SUMMARY OF THE INVENTION

This problem is solved according to the invention by a device for clamping a fluidic component which is subjected to alternating fluid pressure and which comprises a holder within which the fluidic component is arranged. The holder makes contact with the fluidic component at its low pressure end. The device comprises an elastomeric shaped part which surrounds the fluidic component over its entire circumference. The outer contour of the elastomeric shaped part is adapted to the inner contour of the holder and the inner contour of the elastomeric shaped part is adapted to the outer contour of the fluidic component. The elastomeric shaped part has at least one free surface which is exposed to the pressurised fluid. The holder is secured at the high pressure end to a mating part, and

- before the assembly of the device the elastomeric shaped part is chamfered towards the fluidic component on its side facing the fluid pressure, and
- the mating part is provided with an annular projection the outer contour of which is adapted to the inner contour of the holder; after the assembly of the holder with the

mating part the projection projects into the holder and deforms the elastomeric shaped part, as a result of which a uniformly distributed internal tension is generated in the elastomeric shaped part, and

the volume of the projection on the mating part is adapted to the volume that is missing from the elastomeric shaped part in the region of the chamfer, and

the elastomeric shaped part which is deformed and subjected to internal tension after the assembly of the holder with the mating part almost totally fills the space up to the mating part.

The elastomeric shaped part is chamfered into a recess at its high pressure end. The chamfer begins in the outer surface of the high pressure end of the elastomeric shaped part at a solid line which may be, for example, circular, elliptical, or rectangular. The chamfer may, for example, have a constant angle of inclination, or the angle of inclination may vary in the azimuthal direction. In the latter case, it is preferably smaller along the longer side of a cuboid, fluidic component than along the shorter side of the cuboid, fluidic component. The line of intersection of the chamfer with the recess in the elastomeric shaped part may extend at a constant level, or the line of intersection may be curved.

The projection on the mating part may preferably be annular and of constant width. The outer contour of the projection is preferably adapted to the inner contour of the holder. Moreover, the inner contour of the projection may be adapted to the outer contour of the fluidic component. The projection on the mating part may have a constant width and have a constant height on its circumference, or the projection may vary in width and/or height; it may, for example, be higher in the two areas located opposite the two longer sides of a cuboid, fluidic component than in the two areas located opposite the two shorter sides of a cuboid, fluidic component. In this way, the elastomeric shaped part may deform to different degrees in some areas when the holder and mating part are put together and influence the spatial distribution of the internal tension in the elastomeric shaped part. The internal tension in the elastomeric shaped part is produced substantially by the deformation of the elastomeric shaped part, not by its compression. The deformation of the elastomeric shaped part and the distribution of the tension in the elastomeric shaped part can be determined by the finite elements method (FEM).

The elastomeric shaped part is preferably constructed as an injection-molded part. The pre-elastomer is poured without bubbles into a mould that is adapted to the contours of the holder and the fluidic component. An elastomeric shaped part of this kind behaves somewhat like an incompressible fluid. It fits precisely into the holder and fluidic component. The elastomeric shaped part is only exposed to fluid pressure at the pressure end, not at the sides where it abuts on the holder and on the fluidic component. The elastomeric shaped part allows pressure compensation on the fluidic component. The elastomeric shaped part has no free surface towards the low pressure side. The elastomeric shaped part may consist, for example, of natural rubber or synthetic rubber, such as silicon rubber, polyurethane, ethene-propene rubber (EPDM), fluorine rubber (FKM) or nitrile-butadiene rubber (NBR) or of a corresponding rubber.

The fluidic component may consist of a wear-resistant, hard and hence generally brittle material (such as silicon, glass, ceramics, gemstone, e.g., sapphire, ruby, diamond) or of a ductile material with a wear-resistant hard surface (such as plastics, chemically metallized plastics, copper, hard chromium-plated copper, brass, aluminum, steel, steel with a hardened surface, wear-resistant surfaces produced by physical vapor deposition (PVD) or chemical vapor deposition (CVD), for example, titanium nitride (TiN) or polycrystalline diamond on metal and/or plastics. The fluidic component may be made in one piece or composed of a number of pieces, while the pieces may consist of different materials. The fluidic component may contain cavities, voids or channel structures. In the voids there may be microstructures which act as filters or anti-evaporation means, for example. The channels may be nozzle channels for an atomizer nozzle. An atomizer nozzle may contain one or more nozzle channels the axes of which may extend parallel to one another or be inclined relative to one another. If, for example, there are two nozzle channels the axes of which are located in one plane and which intersect outside the nozzle, the two fluid jets that emerge meet at the point of intersection of the axes and the fluid is atomized.

The holder may consist of virtually any desired material, preferably metal or plastics, and may be a body of revolution or a body of any other shape. The holder may, for example, be a pot-shaped body of revolution which contains a rotationally symmetrical recess, starting from its lid end, the axis of which coincides with the axis of the body of revolution. This recess may be cylindrical or in the shape of a truncated cone, the end of the truncated cone with the larger diameter being located at the lid end of the holder. The outer surface of the recess forms the inner contour of the holder. It may be produced as a molding, as a casting or by processing to remove material (e.g., by machining, etching, erosion, elision).

The mating part may consist of metal or plastics.

The holder which contains the elastomeric molding and the fluidic component is assembled with the mating part. The side of the elastomeric shaped part which contains the chamfer faces towards the mating part. The edge of the holder rests on the mating part. The fluidic component may be pushed into the elastomeric shaped part, preferably before the elastomeric shaped part is inserted in the recess in the holder. The holder may be attached to the mating part by screwing, gluing, welding, crimping, casting or press-fitting or snap-fitting onto the mating part. The holder may preferably be secured to the mating part by a union nut.

In a preferred embodiment the mating part is formed as a body of revolution in the area where it is connected to the holder. The fluid which is under high pressure is conducted to the holder through a channel in the mating part which is coaxial, for example. The fluid enters the channel structure in the fluidic component and leaves the fluidic component at the low pressure end thereof in the region of the base of the holder. The fluid pressure acts within the dead volume on the elastomeric shaped part.

The device according to the invention has the following advantages:

The tension within the elastomeric shaped part is spatially more uniformly distributed than the tension which may be produced in the known embodiment of the holder by an annular projection formed on the inside of the holder, underneath which the elastomeric shaped part is pushed during assembly.

The tension within the elastomeric shaped part may be adjusted, not only by the material properties of the shaped part itself, but by the ratio of the volume of the projection on the mating part to the volume which is absent from the tensionless elastomeric shaped part as a result of the chamfer.

The fluidic component is surrounded to its full height by the elastomeric shaped part which is under tension.

The device according to the invention is pressuretight in long-term use at fluctuating pressures with a large dif-

ference between the maximum pressure (40 Mpa or more) and the minimum pressure (about 0.1 Mpa).

The dead volume between the deformed elastomeric shaped part subjected to internal tension and the side of the mating part facing the holder can be kept small. It serves at the same time to equalise the tolerances when the holder is joined to the mating part.

The controlled deformation of the elastomeric shaped part during the joining of the holder to the mating part prevents the elastomeric shaped part from swelling out through the opening in the fluidic component.

The device according to the invention for clamping a fluidic component is used, for example, in a miniaturized high pressure atomizer (e.g., according to WO 91/12687), in a needle-less injector (e.g., according to WO 01/64268) or in an applicator for opthalmologic, medicinal formulations (e.g., according to WO 03/002045). A medicinal fluid administered with a device of this kind may contain a pharmaceutical substance dissolved in a solvent. Suitable solvents include for example water, ethanol, or mixtures thereof. Examples of the pharmaceutical substances include berotec (fenoterol-hydrobromide, atrovent (ipratropium bromide), berodual (combination of fenoterol-hydrobromide and ipratropium bromide), salbutamol (or albuterol), 1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)-ethyl]-amino]-ethanol-hydrobromide), combivent, oxivent (oxitropium-bromide), Ba 679 (tiotropium bromide), BEA 2180 (di-(2-thienyl)glycolic acid-tropenolester), flunisolide, budesonide and others. Examples may be found in WO 97/01329 or WO 98/27959.

DESCRIPTION OF THE INVENTION

The device according to the invention is explained more fully with reference to the Figures:

FIG. **1***a* shows in cross-section and diagonal elevation a pot-shaped holder (**1**) provided with a recess (**2**). An opening (**3**) is provided in the base of the holder.

FIG. **1***b* shows in cross-section and diagonal elevation an elastomeric shaped part (**4**) and a cuboid, fluidic component (**5**), which is made up of two parts and which has been inserted in the elastomeric shaped part. In the contact surface of the two parts a nozzle structure is provided which extends as far as the nozzle aperture (**6**). The top surface of the elastomeric shaped part (**4**) at the high pressure end stands in the annular region (**7**) perpendicular to the axis of the elastomeric shaped part. The chamfer (**8**) of the elastomeric shaped part begins on the top surface of the elastomeric shaped part and extends as far as the outer surface of the fluidic component.

FIG. **1***c* shows in cross section and in diagonal elevation a mating part (**9**) with a bore (**10**) and an annular projection (**11**) on its side facing the elastomeric shaped part.

FIG. **2** shows another embodiment of the projection (**11**) on the mating part (**21**) in diagonal elevation. The projection (**11**) is higher in the two diametrically opposite regions (**22***a*, **22***b*) than in the two diametrically opposite regions (**23***a*, **23***b*). When the holder is joined to the mating part the higher regions (**22***a*, **22***b*) of the projection (**11**) deform the elastomeric shaped part more than the regions (**23***a*, **23***b*).

FIGS. **3***a*, **4***a*, and **5***a* show the elastomeric shaped part viewed perpendicularly. FIGS. **3***b*, **4***b* and **4***b* show cross-sections through the elastomeric shaped part.

The elastomeric shaped part contains a cuboid recess (**31**) for a cuboid fluidic component. The cross-section in FIG. **3***a* runs along the line A-A in FIG. **3***a*; the line A-A runs perpendicularly to the longer side of the recess (**31**). The cross section in FIG. **4***b* runs along the line B-B in FIG. **4***a*; the line B-B runs perpendicularly to the shorter side of the recess (**31**). The cross section in FIG. **5***b* runs along the line C-C in FIG. **5***a*; the line C-C runs diagonally to the recess (**31**). The line of intersection (**32**) of the chamfer (**8**) with the recess (**31**) runs at a constant level. The angle of inclination (measured from the main axis of the component) of the chamfer (**8**) is at its greatest in FIG. **3***b* and at its smallest in FIG. **5***b*, and in FIG. **4***b* the angle of inclination has an intermediate value.

FIG. **6** shows a cross section through the assembled holder which is mounted on a container for a fluid. The holder (**1**) contains in its recess an elastomeric shaped part (**4**) with the fluidic component (**5**). A mating part (**9**) is located on the edge of the holder. The projection (**11**) on the mating part (**9**) projects into the recess in the holder (**1**) and has deformed the elastomeric shaped part (**4**). The side (**61**) of the elastomeric shaped part exposed to the fluid is convex, but the deformed elastomer does not extend right up to the nozzle structure in the fluidic component. The dotted lines (**64** *a*) and (**64** *b*) indicate the contour of the chamfered shaped part (**4**) before the assembly of the holder. The dead volume (**63**) serves to equalize the tolerances during the assembly of the holder; it has been reduced to the minimum. The holder is secured to the mating part (**9**) and to the housing (**65**) for the fluid by a union nut (**62**). The direction of flow of the fluid is indicated by arrows. The low pressure end of the holder is located in the surface which contains the nozzle aperture (**6**). The high pressure in the fluid acts in the channel structure within the fluidic component (**5**), within the dead volume (**63**), within the bore (**10**) in the mating part (**9**) and within the housing that contains the fluid.

FIGS. **7***a*, **7***b*, **7***c* show the holder according to the invention in cross-hatched cross-section and FIGS. **8***a*, **8***b*, and **8***c* compare it with the embodiment in the cross-hatched cross section according to the prior art.

FIG. **7***a* shows a chamfered elastomeric shaped part (**4***a*) with a fluidic component (**5**) inserted therein before the assembly of the holder according to the invention. The elastomeric shaped part is almost as high as the fluidic component at its outer edge but lower in the area of contact with the fluidic component at the recess. The elastomeric shaped part is still un-deformed and is not yet under internal tension. FIG. **7***b* shows the situation after the insertion of a ring (**71**), causing the elastomeric shaped part (**4***b*) to be deformed and internal tension to be produced inside the elastomeric shaped part. The deformed elastomeric shaped part (**4***b*) extends over the fluidic component as far as its upper edge. The convexity of the elastomeric shaped part scarcely projects beyond the height of the fluidic component. FIG. **7***c* shows the deformed elastomeric shaped part (**4***c*) after the assembly of the holder. The inserted projection (**11**) has deformed the elastomeric shaped part (**4***c*). A small dead volume (**63**) is present between the deformed elastomeric shaped part (**4***c*) and the base of the mating part.

FIG. **8***a* shows a (non-chamfered) elastomeric shaped part (**74***a*) with a fluidic component (**5**) inserted therein before the assembly of the holder according to the prior art. The elastomeric shaped part is lower than the fluidic component. The elastomeric shaped part is un-deformed and is not under internal tension. FIG. **8***b* shows the situation after the addition of a ring (**71**) which prevents the elastomeric shaped part (**74***b*) from falling out of the holder or from sliding inside the holder but does not deform the elastomeric shaped part. FIG. **8***c* shows the un-deformed elastomeric shaped part (**74***c*) after the assembly of the holder using a mating part (**9**), on which an annular projection (**11**) is provided. The dead volume (**75**) in FIG. **8***c* is larger than the dead volume (**63**) in FIG. **7***c*.

Example

Mount for an Atomizer Nozzle of Miniature Construction

This device consists of a cylindrical holder made of steel with an external diameter of 6.0 mm and a height of 2.6 mm. It contains a truncated cone-shaped recess with an internal diameter of 4.0 mm at the base of the truncated cone. The base of the holder contains a bore 0.8 mm in diameter. The base of the holder is 0.4 mm thick in the vicinity of the bore.

The outer contour of the elastomeric shaped part made of silicon rubber is cylindrical. Before it is inserted in the holder the cylinder has a diameter of 4.2 mm and is 2.1 mm high on its outer surface. It contains a symmetrically arranged recess 1.3 mm wide and 2.8 mm long which passes axially through the elastomeric shaped part.

The elastomeric shaped part is chamfered towards the recess at its high pressure end. The chamfer begins in the cover surface of the cylinder over a circle with a diameter of 3.2 mm. The chamfer runs at different inclinations towards the rectangular recess to a constant depth of 0.7 mm at the line of intersection with the recess.

The fluidic component is constructed as an atomizer nozzle. The nozzle is a cuboid made up of two sheets of silicon and is 1.4 mm wide, 2.7 mm long, and 2.1 mm high. In the contact surface of the sheets the nozzle contains a recess which is provided with a micro-engineered filter and a micro-engineered evaporation device. On the side of the nozzle where the fluid leaves the nozzle, the recess merges into two channels each of which is 8 μm wide, 6 μm deep, and about 200 μm long. The axes of the two channels are located in one plane and are inclined at about 90 degrees to one another. The two nozzle apertures are spaced from one another by about 100 μm on the outside of the atomizer nozzle.

The essentially cylindrical mating part is provided with an annular projection on its side facing the holder. The projection has an external diameter of 3.15 mm, an internal diameter of 2.9 mm, and a constant height of 0.6 mm. The mating part contains an axial bore 0.4 mm in diameter.

The device is secured to the mating part by means of a union nut. The mating part is part of a container which contains the liquid to be atomized. The liquid is conveyed from the container to the atomizer nozzle by means of a miniaturized high pressure piston pump in amounts of about 15 microliters.

The peak value of the fluid pressure inside the atomizer nozzle is about 65 MPa (650 bar) and falls back to virtually normal air pressure (about 0.1 MPa) after the end of the atomization.

What is claimed is:

1. An apparatus, comprising:

an annular elastomeric part including: (i) an internal passage extending along a central axis from a first end surface thereof to an opposite, second end surface; (ii) a chamfer surface within the internal passage and extending from the first end surface radially inwardly toward the central axis and toward the second end surface thereof, thereby defining an annular rim at a periphery of the first end surface of the annular elastomeric part;

a nozzle including an outer contour and an internal, narrowing nozzle bore extending from a first end to a nozzle aperture at a second end for permitting an aerosol to exit, the nozzle being disposed within the internal passage of the annular elastomeric part such that the first end of the nozzle is adjacent to the chamfer surface of the internal passage; and

a mating element including: (i) a bore for delivering pressurized fluid to the first end of the nozzle, and (ii) an annular projection that engages the annular rim of the annular elastomeric part and deforms the annular elastomeric part at the first end of the nozzle when the annular projection is pressed against the annular rim.

2. The apparatus of claim **1**, wherein at least one of: the chamfer surface is at a constant or varying angle of inclination at each point along the chamfer surface; and a line of intersection of the chamfer surface with the internal passage in the annular elastomeric part extends at a constant level or is curved.

3. The apparatus of claim **1**, wherein the deformation of the annular elastomeric part includes a deformation of the chamfer surface of the annular elastomeric part.

4. The apparatus of claim **1**, further comprising a holder, within which the nozzle and annular elastomeric part are arranged, the holder comprising: (i) an inner surface in contact with the second end of the nozzle, (ii) an inner contour that at least one of mates and aligns with an outer contour of the annular elastomeric part, and (iii) an annular end secured to the mating element with at least one of: screwing, gluing, welding, crimping, casting, press-fitting, snap-fitting, and employing a union-nut.

5. The apparatus of claim **1**, wherein the annular elastomeric part surrounds the outer contour of the nozzle.

6. The apparatus of claim **1**, wherein the projection on the mating element has a width and a height that are independently constant or varying.

7. A method for making a fluidic component clamping assembly, comprising:

inserting a nozzle of the fluidic component into an internal passage of an annular elastomeric part, where:

the annular elastomeric part includes: (i) an internal passage extending along a central axis from a first end surface thereof to an opposite, second end surface; (ii) a chamfer surface within the internal passage and extending from the first end surface radially inwardly toward the central axis and toward the second end surface thereof, thereby defining an annular rim at a periphery of the first end surface of the annular elastomeric part, and

the nozzle includes an outer contour and an internal, narrowing nozzle bore extending from a first end to a nozzle aperture at a second end for permitting an aerosol to exit, the nozzle being disposed within the internal passage of the annular elastomeric part such that the first end of the nozzle is adjacent to the chamfer surface of the internal passage,

engaging a mating element against the annular elastomeric part, where the mating element includes: (i) a bore for delivering pressurized fluid to the first end of the nozzle, and (ii) an annular projection that engages the annular rim of the annular elastomeric part and deforms the annular elastomeric part at the first end of the nozzle when the annular projection is pressed against the annular rim.

8. The method of claim **7**, further comprising:

arranging the nozzle and the annular elastomeric part inside an internal volume of a holder; and

bearing a union member against the holder and engaging a housing such that: (i) the mating element is pressed toward the holder, and (ii) the annular projection of the mating element deforms the annular elastomeric part at the first end of the nozzle as the annular projection is pressed against the annular rim.

9. The method of claim **8**, wherein the annular elastomeric part surrounds the outer contour of the nozzle such that: (i) the first end of the nozzle is in fluid communication with, and receives the pressurized fluid from, the bore of the mating element, and (ii) both the first end of the nozzle and the adjacent first end surface of the annular elastomeric part are spaced away from the bore of the mating element, thereby defining an unoccupied volume within the internal volume of the holder, and exposing the first end surface of the annular elastomeric part to the pressurized fluid.

10. The method of claim **7**, further comprising deforming the chamfer surface of the annular elastomeric part as the annular projection is pressed against the annular rim.

11. The method of claim **7**, further comprising internally tensioning the annular elastomeric part via the annular projection of the mating element such that the internal tension is substantially uniformly distributed.

* * * * *

EXHIBIT D

US007837235B2

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

(10) **Patent No.: US 7,837,235 B2**
(45) **Date of Patent: Nov. 23, 2010**

(54) **DEVICE FOR CLAMPING A FLUIDIC COMPONENT**

(75) Inventors: **Johannes Geser**, Ingelheim (DE); **Matthias Hausmann**, Dortmund (DE)

(73) Assignee: **Boehringer Ingelheim International GmbH**, Ingelheim am Rhein (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1161 days.

(21) Appl. No.: **11/031,171**

(22) Filed: **Jan. 7, 2005**

(65) **Prior Publication Data**

US 2005/0194472 A1 Sep. 8, 2005

(30) **Foreign Application Priority Data**

Jan. 8, 2004 (DE) 10 2004 001 451

(51) **Int. Cl.**
F16L 25/00 (2006.01)

(52) **U.S. Cl.** **285/332.2**; 285/249; 285/331; 285/334.3; 285/382.5

(58) **Field of Classification Search** 285/249, 285/332, 332.1–332.4, 334.1, 334.3, 382.4, 285/382.5, 331
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,181,060	A *	4/1916	Bennett	277/625
2,278,479	A *	4/1942	Parker	285/54
2,331,020	A *	10/1943	Frances	285/295.2
2,669,465	A *	2/1954	Newell	285/53
3,249,372	A *	5/1966	Pollack	285/332.3
3,747,960	A *	7/1973	Bawa	285/39
3,757,960	A	9/1973	Hill et al.	
3,997,111	A	12/1976	Thomas et al.	
4,073,157	A *	2/1978	Aylmer et al.	405/170
4,150,794	A	4/1979	Higgins	
4,244,521	A	1/1981	Guse	
4,313,570	A	2/1982	Olsen	
5,033,681	A	7/1991	Munoz	
5,497,944	A	3/1996	Weston et al.	
5,848,753	A	12/1998	Wands et al.	
5,964,416	A	10/1999	Jaeger et al.	
6,176,442	B1	1/2001	Eicher	
6,223,933	B1	5/2001	Hochrainer et al.	

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2291737	A1	12/1998

(Continued)

OTHER PUBLICATIONS

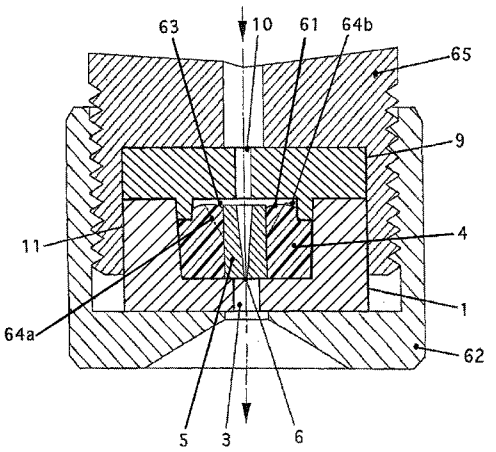
International Search Report for PCT/EP2004/014764 mailed Apr. 15, 2004.

Primary Examiner—Aaron Dunwoody
Assistant Examiner—Fannie Kee
(74) *Attorney, Agent, or Firm*—Michael P. Morris; David L. Kershner

(57) **ABSTRACT**

A fluidic component is arranged in an elastomeric shaped part, the contour of which is matched to the outer contour of the component and to the inner contour of a holder. The elastomeric shaped part is chamfered towards the fluidic component on its pressure side. When the holder is assembled, the elastomeric shaped part is deformed by a projection provided on a mating part and is put under uniformly distributed internal tension, after which the elastomeric shaped part surrounds the fluidic component to its full height.

9 Claims, 4 Drawing Sheets



U.S. PATENT DOCUMENTS

6,481,435	B2	11/2002	Hochrainer et al.
6,491,897	B1	12/2002	Freund
6,685,691	B1	2/2004	Freund et al.
6,846,413	B1	1/2005	Kadel et al.
6,977,042	B2	12/2005	Kadel et al.
6,986,346	B2	1/2006	Hochrainer et al.
7,040,311	B2	5/2006	Hochrainer et al.
7,090,093	B2	8/2006	Hochrainer et al.
7,314,187	B2	1/2008	Hochrainer
2001/0008632	A1	7/2001	Freund et al.
2001/0032642	A1	10/2001	Bach et al.
2002/0007155	A1	1/2002	Freund et al.
2003/0064032	A1	4/2003	Lamche et al.
2003/0066524	A1	4/2003	Hochrainer et al.
2004/0010239	A1	1/2004	Hochrainer
2004/0143235	A1	7/2004	Freund et al.
2004/0159319	A1	8/2004	Kadel et al.
2004/0182867	A1	9/2004	Hochrainer et al.
2005/0001076	A1	1/2005	Eicher et al.
2005/0032494	A1	2/2005	Swant
2005/0159441	A1	7/2005	Hochrainer et al.
2005/0263618	A1	12/2005	Spallek et al.
2006/0196500	A1	9/2006	Hochrainer et al.
2006/0239930	A1	10/2006	Lamche et al.
2006/0258993	A1	11/2006	Hochrainer et al.
2006/0285987	A1	12/2006	Jaeger et al.
2009/0114215	A1	5/2009	Boeck et al.
2009/0185983	A1	7/2009	Freund et al.

FOREIGN PATENT DOCUMENTS

CA	2404360	A1	9/2001
CA	2653183	A1	12/2007
CA	2653422	A1	12/2007
DE	4115131	A1	11/1991
DE	19722338	A1	12/1998
EP	0046664		3/1982
WO	9114468		10/1991
WO	WO 94/07607		4/1994
WO	9701329		1/1997
WO	9712683		4/1997
WO	9712687		4/1997
WO	9827959		7/1998
WO	9916530		4/1999
WO	0164268		9/2001
WO	03002045		1/2003
WO	2005065836	A1	7/2005
WO	2007141201	A1	12/2007
WO	2007141203	A1	12/2007

* cited by examiner

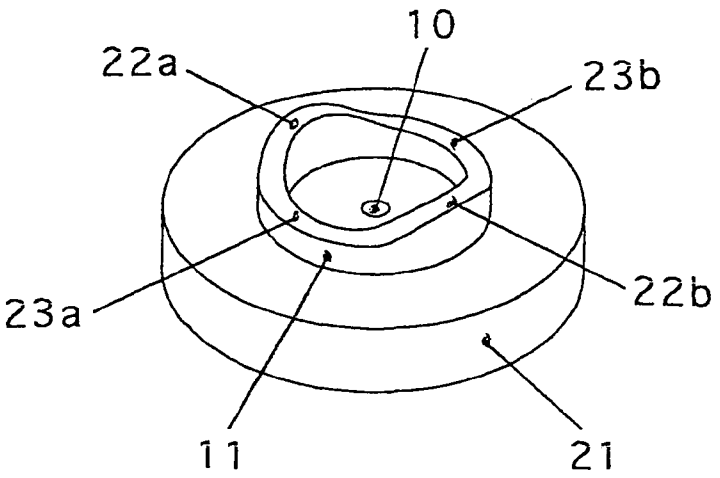


Fig. 2

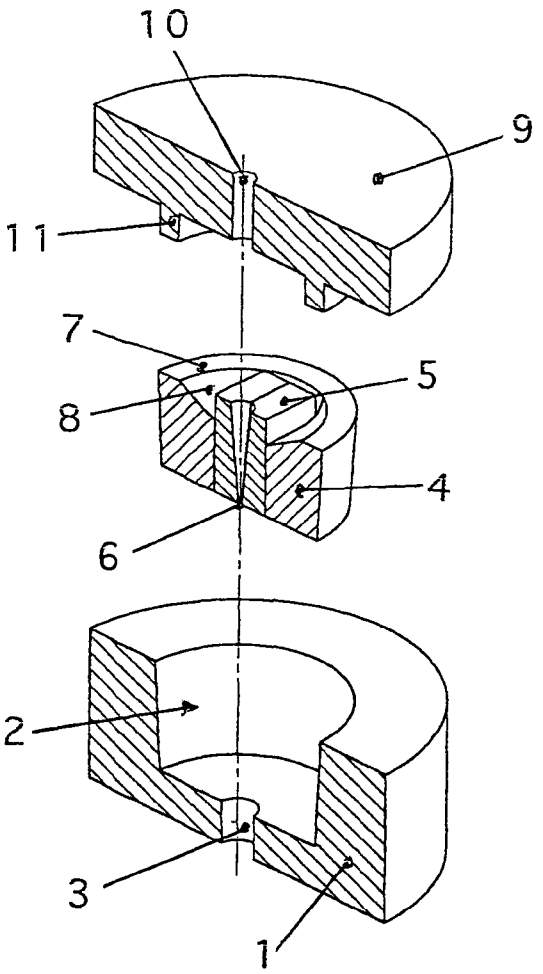


Fig. 1c

Fig. 1b

Fig. 1a

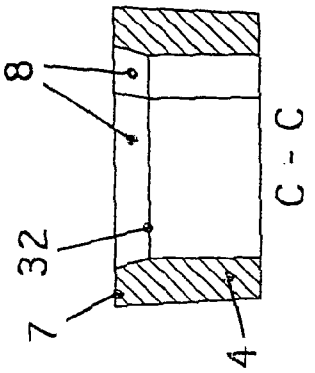


Fig. 5b

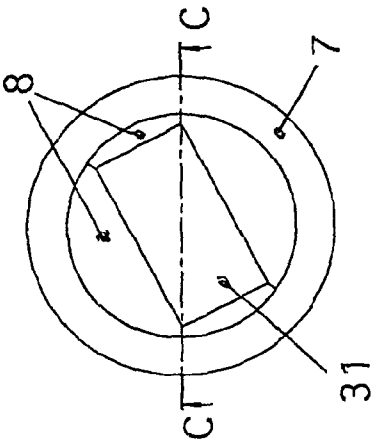


Fig. 5a

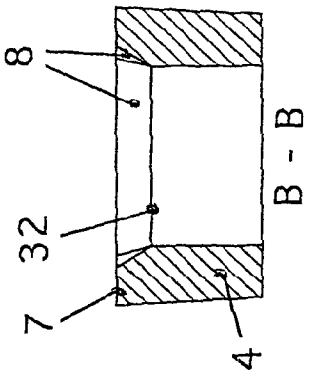


Fig. 4b

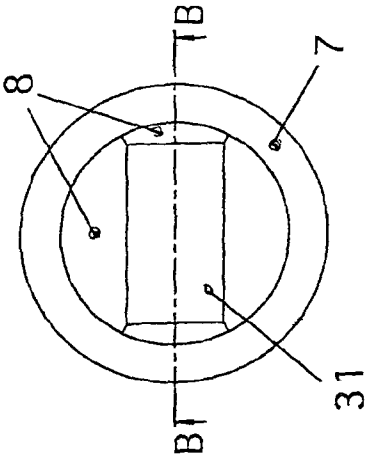


Fig. 4a

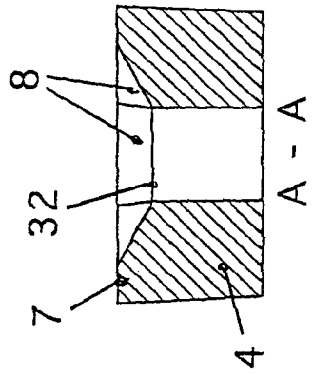


Fig. 3b

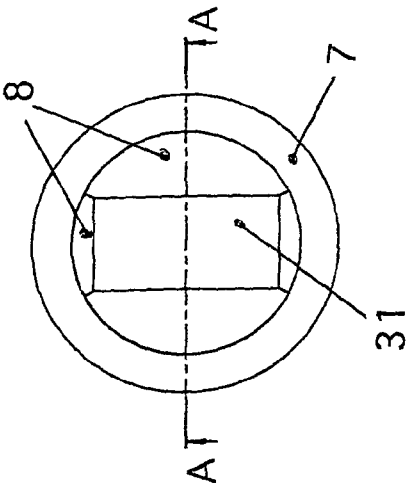
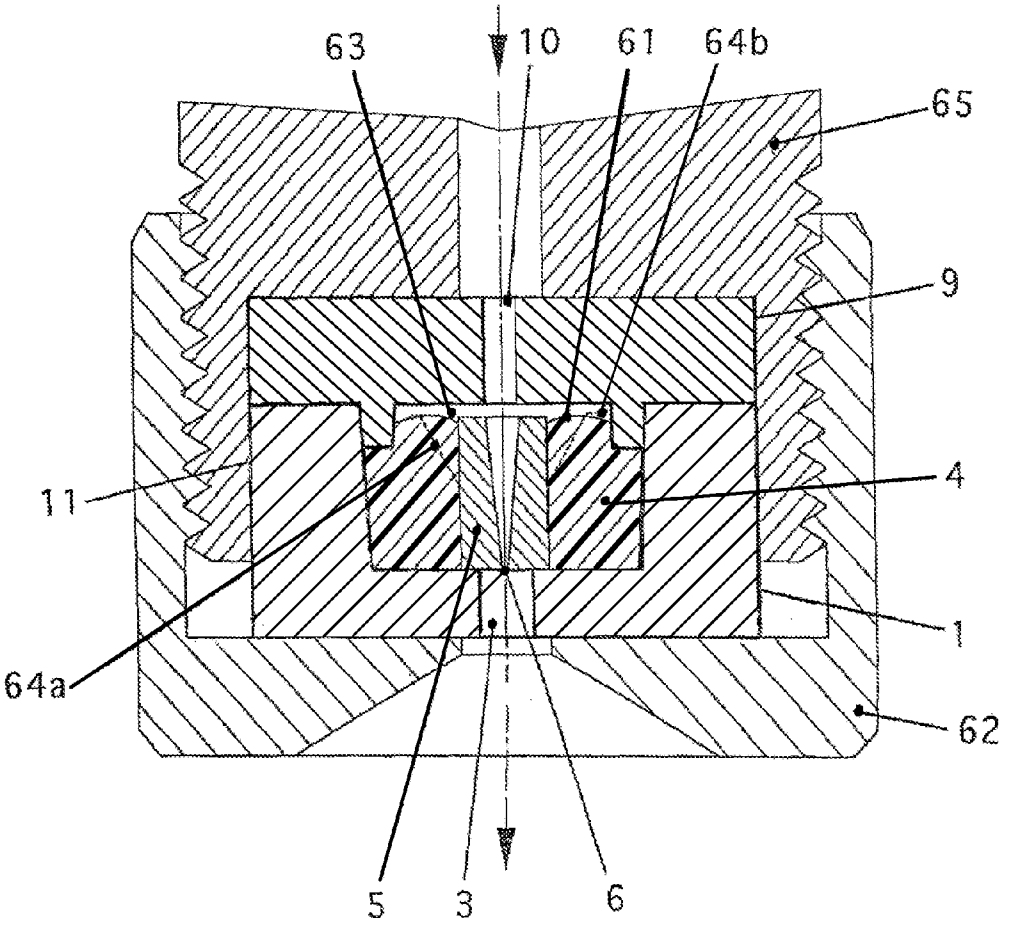


Fig. 3a

FIG. 6



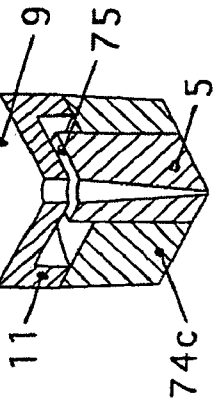


Fig. 8c
Prior Art

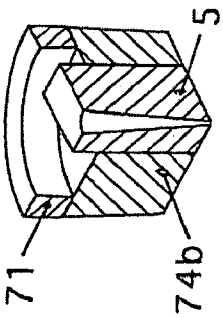


Fig. 8b
Prior Art

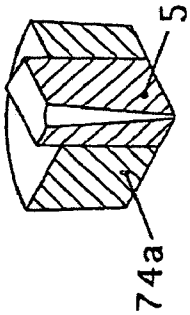


Fig. 8a
Prior Art

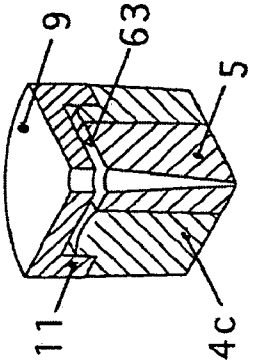


Fig. 7c

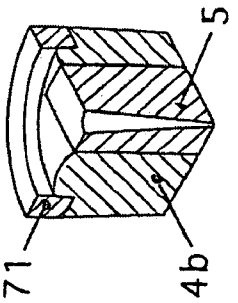


Fig. 7b

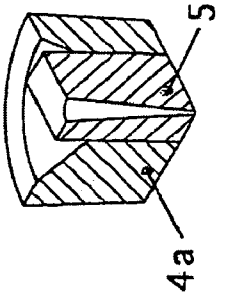


Fig. 7a

DEVICE FOR CLAMPING A FLUIDIC COMPONENT

BACKGROUND OF THE INVENTION

1.Field of the Invention

The invention relates to a device for clamping a fluidic component, particularly a nozzle, particularly in the high pressure region. Of particular interest are holders for micro-engineered components, particularly micro-engineered nozzles which are to be produced by micro-engineering. Such nozzles are used for example in nebulizers for producing propellant-free medicinal aerosols used for inhalation.

The aim of the invention is to further improve the clamping of a fluidic component consisting of a wear-resistant, hard, and generally brittle material, and to increase the reliability of the holder.

2.Brief Description of the Prior Art

Micro-engineered nozzles having for example a nozzle aperture of less than 10 μm are described for example in WO 94/07607 and WO 99/16530.The inhalable droplets produced thereby have a mean diameter of about 5 μm, when the pressure of the liquid to be nebulized is from 5 MPa (50 bar) to 40 MPa (400 bar). The nozzles may for example be made from thin sheets of silicon and glass. The external dimensions of the nozzles are in the millimeter range. A typical nozzle consists for example of a cuboid with sides measuring 1.1 mm, 1.5 mm and 2.0 mm, made up of two sheets. Nebulizers for producing propellant-free aerosols in which the device according to the invention for clamping a fluidic component can be used are known from WO 91/14468 or WO 97/12687.

The term fluidic component denotes a component which is exposed to a pressurized fluid, and the pressure is also present inside the component, for example in a nozzle bore. Such a component may be kept pressure-tight for example by pressing into a holder of hard material if the material of the component can withstand mechanical forces without collapsing or deforming to an unacceptable degree. At high pressures, seals of deformable material, e.g. copper, or hard material which can be pressed in with great force are used. In the case of components made of brittle material the known processes for pressure-tight clamping of the component require considerable effort and great care. It is impossible to predict with any reliability the service life of a fluidic component clamped in this way.

U.S. Pat. No. 3,997,111 describes a fluid jet cutting device with which a high-speed fluid jet is produced which is used for cutting, drilling or machining material. The nozzle body is cylindrical and consists e.g. of sapphire or corundum. The setting ring is pressed into an annular recess in the nozzle carrier and seals off the nozzle body against the nozzle carrier.

U.S. Pat. No. 4,313,570 describes a nozzle holder for a water jet cutting device wherein the nozzle body is surrounded by a ring of elastomeric material which is in turn mounted in a recess in the holder. The recess is in the form of a straight cylinder. The cross-section of the ring is rectangular. The outer surface of the recess and the outer and inner surfaces of the ring are arranged concentrically to the axis of the nozzle body and run parallel to one another and to the axis of the nozzle body.

WO 97/12683 discloses a device for clamping a fluidic component which is subjected to fluid pressure, which is suitable for components consisting of a wear-resistant, hard and hence generally brittle material, and which does not produce any excessively great local material tensions in the component. The fluidic component is arranged in a holder which makes contact with the fluidic component on its low pressure side. The fluidic component is surrounded by an elastomeric shaped part the outer contour of which is adapted to the inner contour of the holder and the inner contour of which is adapted to the outer contour of the fluidic component. The elastomeric component surrounds the entire circumference of the fluidic component. At least one free surface of the elastomeric component is exposed to the pressurized fluid. The holder may have a projection on the inside underneath which the elastomeric shaped part is pushed. It has proved difficult to generate internal tension in the elastomeric shaped part which is sufficiently great, even at low fluid pressures, and which is spatially roughly uniformly distributed in the elastomeric shaped part.

This known device has proved pressure-tight when subjected substantially constantly to moderate and high fluid pressures. When subjected to alternating fluid pressures fluctuating between a high peak value and a very low value, the known device is in need of improvement for long-term use.

The problem thus arises of providing a device for clamping a fluidic component which is reliably leak-tight even when subjected to alternating loading from a sharply fluctuating fluid pressure in long-term use. The components needed should be cheap to manufacture and should also be capable of being assembled with relative ease.

BREIF DESCRIPTION OF THE DRAWINGS

FIG. **1***a* is a cross-sectional, elevational view of a pot-shaped holder (**1**).

FIG. **1***b* is a cross-sectional, elevational view of an elastomeric shaped part (**4**) and a cuboid, fluidic component (**5**).

FIG. **1***c* is a cross-sectional, elevational view of a mating part (**9**) with a bore (**10**) and an annular projection (**11**).

FIG. **2** is an elevational view of the underside of the mating part (**9**).

FIGS. **3***a*, **4***a*, and **5***a* show the elastomeric shaped part viewed perpendicularly.

FIGS. **3***b*, **4***b*, and **5***b* are cross-sections through the elastomeric shaped part.

FIGS. **7***a*, **7***b*, and **7***c* show the holder according to the invention in cross-hatched cross-section.

FIGS. **8***a*, **8***b*, and **8***c* show a prior-art embodiment.

SUMMARY OF THE INVENTION

This problem is solved according to the invention by a device for clamping a fluidic component which is subjected to alternating fluid pressure and which comprises a holder within which the fluidic component is arranged. The holder makes contact with the fluidic component at its low pressure end. The device comprises an elastomeric shaped part which surrounds the fluidic component over its entire circumference. The outer contour of the elastomeric shaped part is adapted to the inner contour of the holder and the inner contour of the elastomeric shaped part is adapted to the outer contour of the fluidic component. The elastomeric shaped part has at least one free surface which is exposed to the pressurised fluid. The holder is secured at the high pressure end to a mating part, and

- before the assembly of the device the elastomeric shaped part is chamfered towards the fluidic component on its side facing the fluid pressure, and
- the mating part is provided with an annular projection the outer contour of which is adapted to the inner contour of the holder; after the assembly of the holder with the mating part the projection projects into the holder and deforms the elastomeric shaped part, as a result of which

a uniformly distributed internal tension is generated in the elastomeric shaped part, and

the volume of the projection on the mating part is adapted to the volume that is missing from the elastomeric shaped part in the region of the chamfer, and

the elastomeric shaped part which is deformed and subjected to internal tension after the assembly of the holder with the mating part almost totally fills the space up to the mating part.

The elastomeric shaped part is chamfered into a recess at its high pressure end. The chamfer begins in the outer surface of the high pressure end of the elastomeric shaped part at a solid line which may be, for example, circular, elliptical, or rectangular. The chamfer may, for example, have a constant angle of inclination, or the angle of inclination may vary in the azimuthal direction. In the latter case, it is preferably smaller along the longer side of a cuboid, fluidic component than along the shorter side of the cuboid, fluidic component. The line of intersection of the chamfer with the recess in the elastomeric shaped part may extend at a constant level, or the line of intersection may be curved.

The projection on the mating part may preferably be annular and of constant width. The outer contour of the projection is preferably adapted to the inner contour of the holder. Moreover, the inner contour of the projection may be adapted to the outer contour of the fluidic component. The projection on the mating part may have a constant width and have a constant height on its circumference, or the projection may vary in width and/or height; it may, for example, be higher in the two areas located opposite the two longer sides of a cuboid, fluidic component than in the two areas located opposite the two shorter sides of a cuboid, fluidic component. In this way, the elastomeric shaped part may deform to different degrees in some areas when the holder and mating part are put together and influence the spatial distribution of the internal tension in the elastomeric shaped part. The internal tension in the elastomeric shaped part is produced substantially by the deformation of the elastomeric shaped part, not by its compression. The deformation of the elastomeric shaped part and the distribution of the tension in the elastomeric shaped part can be determined by the finite elements method (FEM).

The elastomeric shaped part is preferably constructed as an injection-molded part. The pre-elastomer is poured without bubbles into a mould that is adapted to the contours of the holder and the fluidic component. An elastomeric shaped part of this kind behaves somewhat like an incompressible fluid. It fits precisely into the holder and fluidic component. The elastomeric shaped part is only exposed to fluid pressure at the pressure end, not at the sides where it abuts on the holder and on the fluidic component. The elastomeric shaped part allows pressure compensation on the fluidic component. The elastomeric shaped part has no free surface towards the low pressure side. The elastomeric shaped part may consist, for example, of natural rubber or synthetic rubber, such as silicon rubber, polyurethane, ethene-propene rubber (EPDM), fluorine rubber (FKM) or nitrile-butadiene rubber (NBR) or of a corresponding rubber.

The fluidic component may consist of a wear-resistant, hard and hence generally brittle material (such as silicon, glass, ceramics, gemstone, e.g., sapphire, ruby, diamond) or of a ductile material with a wear-resistant hard surface (such as plastics, chemically metallized plastics, copper, hard chromium-plated copper, brass, aluminum, steel, steel with a hardened surface, wear-resistant surfaces produced by physical vapor deposition (PVD) or chemical vapor deposition (CVD), for example, titanium nitride (TiN) or polycrystalline diamond on metal and/or plastics. The fluidic component may be made in one piece or composed of a number of pieces, while the pieces may consist of different materials. The fluidic component may contain cavities, voids or channel structures. In the voids there may be microstructures which act as filters or anti-evaporation means, for example. The channels may be nozzle channels for an atomizer nozzle. An atomizer nozzle may contain one or more nozzle channels the axes of which may extend parallel to one another or be inclined relative to one another. If, for example, there are two nozzle channels the axes of which are located in one plane and which intersect outside the nozzle, the two fluid jets that emerge meet at the point of intersection of the axes and the fluid is atomized.

The holder may consist of virtually any desired material, preferably metal or plastics, and may be a body of revolution or a body of any other shape. The holder may, for example, be a pot-shaped body of revolution which contains a rotationally symmetrical recess, starting from its lid end, the axis of which coincides with the axis of the body of revolution. This recess may be cylindrical or in the shape of a truncated cone, the end of the truncated cone with the larger diameter being located at the lid end of the holder. The outer surface of the recess forms the inner contour of the holder. It may be produced as a molding, as a casting or by processing to remove material (e.g., by machining, etching, erosion, elision).

The mating part may consist of metal or plastics.

The holder which contains the elastomeric molding and the fluidic component is assembled with the mating part. The side of the elastomeric shaped part which contains the chamfer faces towards the mating part. The edge of the holder rests on the mating part. The fluidic component may be pushed into the elastomeric shaped part, preferably before the elastomeric shaped part is inserted in the recess in the holder. The holder may be attached to the mating part by screwing, gluing, welding, crimping, casting or press-fitting or snap-fitting onto the mating part. The holder may preferably be secured to the mating part by a union nut.

In a preferred embodiment the mating part is formed as a body of revolution in the area where it is connected to the holder. The fluid which is under high pressure is conducted to the holder through a channel in the mating part which is coaxial, for example. The fluid enters the channel structure in the fluidic component and leaves the fluidic component at the low pressure end thereof in the region of the base of the holder. The fluid pressure acts within the dead volume on the elastomeric shaped part.

The device according to the invention has the following advantages:

The tension within the elastomeric shaped part is spatially more uniformly distributed than the tension which may be produced in the known embodiment of the holder by an annular projection formed on the inside of the holder, underneath which the elastomeric shaped part is pushed during assembly.

The tension within the elastomeric shaped part may be adjusted, not only by the material properties of the shaped part itself, but by the ratio of the volume of the projection on the mating part to the volume which is absent from the tensionless elastomeric shaped part as a result of the chamfer.

The fluidic component is surrounded to its full height by the elastomeric shaped part which is under tension.

The device according to the invention is pressuretight in long-term use at fluctuating pressures with a large difference between the maximum pressure (40 Mpa or more) and the minimum pressure (about 0.1 Mpa).

The dead volume between the deformed elastomeric shaped part subjected to internal tension and the side of the mating part facing the holder can be kept small. It serves at the same time to equalise the tolerances when the holder is joined to the mating part.

The controlled deformation of the elastomeric shaped part during the joining of the holder to the mating part prevents the elastomeric shaped part from swelling out through the opening in the fluidic component.

The device according to the invention for clamping a fluidic component is used, for example, in a miniaturized high pressure atomizer (e.g., according to WO 91/12687), in a needle-less injector (e.g., according to WO 01/64268) or in an applicator for ophthalmologic, medicinal formulations (e.g., according to WO 03/002045). A medicinal fluid administered with a device of this kind may contain a pharmaceutical substance dissolved in a solvent. Suitable solvents include for example water, ethanol, or mixtures thereof. Examples of the pharmaceutical substances include berotec (fenoterol-hydrobromide, atrovent (ipratropium bromide), berodual (combination of fenoterol-hydrobromide and ipratropium bromide), salbutamol (or albuterol), 1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)-ethyl]-amino]-ethanol-hydrobromide), combivent, oxivent (oxitropium-bromide), Ba 679 (tiotropium bromide), BEA 2180 (di-(2-thienyl)glycolic acid-tropenolester), flunisolide, budesonide and others. Examples may be found in WO 97/01329 or WO 98/27959.

DESCRIPTION OF THE INVENTION

The device according to the invention is explained more fully with reference to the Figures:

FIG. **1***a* shows in cross-section and diagonal elevation a pot-shaped holder (**1**) provided with a recess (**2**). An opening (**3**) is provided in the base of the holder.

FIG. **1***b* shows in cross-section and diagonal elevation an elastomeric shaped part (**4**) and a cuboid, fluidic component (**5**), which is made up of two parts and which has been inserted in the elastomeric shaped part. In the contact surface of the two parts a nozzle structure is provided which extends as far as the nozzle aperture (**6**). The top surface of the elastomeric shaped part (**4**) at the high pressure end stands in the annular region (**7**) perpendicular to the axis of the elastomeric shaped part. The chamfer (**8**) of the elastomeric shaped part begins on the top surface of the elastomeric shaped part and extends as far as the outer surface of the fluidic component.

FIG. **1***c* shows in cross section and in diagonal elevation a mating part (**9**) with a bore (**10**) and an annular projection (**11**) on its side facing the elastomeric shaped part.

FIGS. **3***a*, **4***a*, and **5***a* show the elastomeric shaped part viewed perpendicularly.

FIGS. **3***b*, **4***b*, and **5***b* show cross-sections through the elastomeric shaped part.

The elastomeric shaped part contains a cuboid recess (**31**) for a cuboid fluidic component. The cross-section in FIG. **3***b* runs along the line A-A in FIG. **3***a*; the line A-A runs perpendicularly to the longer side of the recess (**31**). The cross section in FIG. **4***b* runs along the line B-B in FIG. **4***a*; the line B-B runs perpendicularly to the shorter side of the recess (**31**). The cross section in FIG. **5***b* runs along the line C-C in FIG. **5***a*; the line C-C runs diagonally to the recess (**31**). The line of intersection (**32**) of the chamfer (**8**) with the recess (**31**) runs at a constant level. The angle of inclination (measured from the main axis of the component) of the chamfer (**8**) is at its greatest in FIG. **3***b* and at its smallest in FIG. **5***b* and in FIG. **4***b* the angle of inclination has an intermediate value.

FIG. **6** shows a cross section through the assembled holder which is mounted on a container for a fluid. The holder (**1**) contains in its recess an elastomeric shaped part (**4**) with the fluidic component (**5**). A mating part (**9**) is located on the edge of the holder. The projection (**11**) on the mating part (**9**) projects into the recess in the holder (**1**) and has deformed the elastomeric shaped part (**4**). The side (**61**) of the elastomeric shaped part exposed to the fluid is convex, but the deformed elastomer does not extend right up to the nozzle structure in the fluidic component. The dotted lines (**64***a*) and (**64***b*) indicate the contour of the chamfered shaped part (**4**) before the assembly of the holder. The dead volume (**63**) serves to equalize the tolerances during the assembly of the holder; it has been reduced to the minimum. The holder is secured to the mating part (**9**) and to the housing (**65**) for the fluid by a union nut (**62**). The direction of flow of the fluid is indicated by arrows. The low pressure end of the holder is located in the surface which contains the nozzle aperture (**6**). The high pressure in the fluid acts in the channel structure within the fluidic component (**5**), within the dead volume (**63**), within the bore (**10**) in the mating part (**9**) and within the housing that contains the fluid.

FIGS. **7***a*, **7***b*, and **7***c* show the holder according to the invention in cross-hatched cross-section and FIGS. **8***a*, **8***b*, and **8***c* compare it with the embodiment in the cross-hatched cross section according to the prior art.

FIG. **7***a* shows a chamfered elastomeric shaped part (**4***a*) with a fluidic component (**5**) inserted therein before the assembly of the holder according to the invention. The elastomeric shaped part is almost as high as the fluidic component at its outer edge but lower in the area of contact with the fluidic component at the recess. The elastomeric shaped part is still un-deformed and is not yet under internal tension. FIG. **7***b* shows the situation after the insertion of a ring (**71**), causing the elastomeric shaped part (**4***b*) to be deformed and internal tension to be produced inside the elastomeric shaped part. The deformed elastomeric shaped part (**4***b*) extends over the fluidic component as far as its upper edge. The convexity of the elastomeric shaped part scarcely projects beyond the height of the fluidic component. FIG. **7***c* shows the deformed elastomeric shaped part (**4***c*) after the assembly of the holder. The inserted projection (**11**) has deformed the elastomeric shaped part (**4***c*). A small dead volume (**63**) is present between the deformed elastomeric shaped part (**4***c*) and the base of the mating part.

FIG. **8***a* shows a (non-chamfered) elastomeric shaped part (**74***a*) with a fluidic component (**5**) inserted therein before the assembly of the holder according to the prior art. The elastomeric shaped part is lower than the fluidic component. The elastomeric shaped part is un-deformed and is not under internal tension. FIG. **8***b* shows the situation after the addition of a ring (**71**) which prevents the elastomeric shaped part (**74***b*) from falling out of the holder or from sliding inside the holder but does not deform the elastomeric shaped part. FIG. **8***c* shows the un-deformed elastomeric shaped part (**74***c*) after the assembly of the holder using a mating part (**9**), on which an annular projection (**11**) is provided. The dead volume (**75**) in FIG. **8***c* is larger than the dead volume (**63**) in FIG. **7***c*.

EXAMPLE

Mount for an Atomizer Nozzle of Miniature Construction

This device consists of a cylindrical holder made of steel with an external diameter of 6.0 mm and a height of 2.6 mm. It contains a truncated cone-shaped recess with an internal

diameter of 4.0 mm at the base of the truncated cone. The base of the holder contains a bore 0.8 mm in diameter. The base of the holder is 0.4 mm thick in the vicinity of the bore.

The outer contour of the elastomeric shaped part made of silicon rubber is cylindrical. Before it is inserted in the holder the cylinder has a diameter of 4.2 mm and is 2.1 mm high on its outer surface. It contains a symmetrically arranged recess 1.3 mm wide and 2.8 mm long which passes axially through the elastomeric shaped part.

The elastomeric shaped part is chamfered towards the recess at its high pressure end. The chamfer begins in the cover surface of the cylinder over a circle with a diameter of 3.2 mm. The chamfer runs at different inclinations towards the rectangular recess to a constant depth of 0.7 mm at the line of intersection with the recess.

The fluidic component is constructed as an atomizer nozzle. The nozzle is a cuboid made up of two sheets of silicon and is 1.4 mm wide, 2.7 mm long, and 2.1 mm high. In the contact surface of the sheets the nozzle contains a recess which is provided with a micro-engineered filter and a micro-engineered evaporation device. On the side of the nozzle where the fluid leaves the nozzle, the recess merges into two channels each of which is 8 μm wide, 6 μm deep, and about 200 μm long. The axes of the two channels are located in one plane and are inclined at about 90 degrees to one another. The two nozzle apertures are spaced from one another by about 100 μm on the outside of the atomizer nozzle.

The essentially cylindrical mating part is provided with an annular projection on its side facing the holder. The projection has an external diameter of 3.15 mm, an internal diameter of 2.9 mm, and a constant height of 0.6 mm. The mating part contains an axial bore 0.4 mm in diameter.

The device is secured to the mating part by means of a union nut. The mating part is part of a container which contains the liquid to be atomized. The liquid is conveyed from the container to the atomizer nozzle by means of a miniaturized high pressure piston pump in amounts of about 15 microliters.

The peak value of the fluid pressure inside the atomizer nozzle is about 65 MPa (650 bar) and falls back to virtually normal air pressure (about 0.1 MPa) after the end of the atomization.

What is claimed is:

1. An apparatus, comprising:

a housing including a bore for delivering pressurized fluid;

a holder including an internal volume;

a mating element that engages the holder and covers the internal volume thereof, the mating element including: (i) a bore in fluid communication with the bore of the housing for delivering the pressurized fluid into the internal volume of the holder, and (ii) an annular projection that extends into the internal volume of the holder;

a nozzle including an outer contour and an internal, narrowing nozzle bore extending from a first end to a nozzle aperture at a second end through which an aerosol exits;

an annular elastomeric part surrounding the outer contour of the nozzle and being disposed in the internal volume of the holder such that: (i) the first end of the nozzle is in fluid communication with, and receives the pressurized fluid from, the bore of the mating element, and (ii) both the first end of the nozzle and an adjacent end surface of the annular elastomeric part are spaced away from the bore of the mating element, thereby defining an unoccupied volume within the internal volume of the holder, and exposing the end surface of the annular elastomeric part to the pressurized fluid; and

a union member bearing against the holder and engaging the housing such that: (i) the mating element is pressed toward the holder, and (ii) the annular projection of the mating element deforms the annular elastomeric part at the first end of the nozzle.

2. The apparatus according to claim **1**, wherein the annular projection of the mating element internally tensions the annular elastomeric part such that the internal tension is substantially uniformly distributed.

3. The apparatus of claim **1**, wherein the annular elastomeric part includes an internal passage in which the nozzle is disposed such that the annular elastomeric part surrounds the outer contour of the nozzle.

4. The apparatus of claim **3**, wherein the internal passage extends from the end surface of the annular elastomeric part to an opposite end thereof.

5. The apparatus of claim **4**, wherein the internal passage includes a chamfer surface at the end surface of the annular elastomeric part that would not bear against the nozzle absent the deformation of the annular elastomeric part by the annular projection of the mating element.

6. The apparatus according to claim **5**, wherein the chamfer surface is chamfered at a constant or varying angle of inclination at each point along the chamfer surface absent the deformation of the annular elastomeric part by the annular projection of the mating element.

7. The apparatus according to claim **5**, wherein a line of intersection of the chamfer surface with the internal passage of the annular elastomeric part extends at a constant level or is curved.

8. The apparatus according to claim **1**, wherein the annular projection on the mating element has a width and a height that are independently constant or varying along a length of the annular projection.

9. The apparatus according to claim **1**, wherein the holder further includes: (i) an inside surface in contact with the second end of the nozzle, (ii) an inside contour that mates and/or aligns with an outside contour of the annular elastomeric part, and (iii) an annular end secured to the mating element.

* * * * *

EXHIBIT E

US008733341B2

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

(10) **Patent No.: US 8,733,341 B2**
(45) **Date of Patent: May 27, 2014**

(54) **ATOMIZER AND METHOD OF ATOMIZING FLUID WITH A NOZZLE RINSING MECHANISM**

(75) Inventors: **Georg Boeck**, Laupheim (DE); **Michael Spallek**, Ingelheim (DE)

(73) Assignee: **Boehringer Ingelheim International GmbH**, Ingelheim am Rhein (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1148 days.

(21) Appl. No.: **12/299,650**

(22) PCT Filed: **Apr. 16, 2007**

(86) PCT No.: **PCT/EP2007/003322**

§ 371 (c)(1),
(2), (4) Date: **Dec. 24, 2008**

(87) PCT Pub. No.: **WO2007/128381**

PCT Pub. Date: **Nov. 15, 2007**

(65) **Prior Publication Data**

US 2009/0114215 A1 May 7, 2009

(30) **Foreign Application Priority Data**

May 10, 2006 (DE) 10 2006 022 002

(51) **Int. Cl.**
A61M 15/00 (2006.01)
A61M 15/02 (2006.01)
A61M 11/00 (2006.01)

(52) **U.S. Cl.**
USPC **128/200.14**; 128/200.17; 128/200.21; 128/203.15; 128/203.23

(58) **Field of Classification Search**
USPC 128/200.14–200.23, 203.15, 203.19, 128/203.21, 204.25; 222/148, 149, 153.11, 222/153.12, 319, 464.3; 604/68–72, 604/122–127
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,157,179	A *	11/1964	Allen et al.	128/200.23
3,675,825	A *	7/1972	Morane	222/148
4,048,997	A *	9/1977	Raghavachari et al.	604/189
5,433,343	A *	7/1995	Meshberg	222/25
5,497,944	A	3/1996	Weston	
5,593,069	A *	1/1997	Jinks	222/246
5,662,098	A *	9/1997	Yoshida	128/200.22
5,662,271	A	9/1997	Weston	
5,833,088	A	11/1998	Kladders	
5,964,416	A	10/1999	Jaeger	
6,401,987	B1	6/2002	Oechsel et al.	
6,402,055	B1	6/2002	Jaeger et al.	

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2297174 A1	2/1999
DE	19733651 A1	2/1999

(Continued)

OTHER PUBLICATIONS

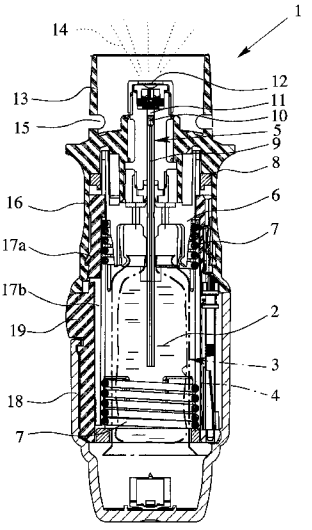
International Search Report for PCT/EP2007/003322 mailed Aug. 17, 2007.

Primary Examiner — Justine Yu
Assistant Examiner — Douglas Sul
(74) *Attorney, Agent, or Firm* — Michael P. Morris; Mary-Ellen M. Devlin

(57) **ABSTRACT**

An atomizer and a method of dispensing and atomizing fluid into individual containers through a nozzle are proposed, where in order to improve the dosing accuracy, a preliminary amount of fluid, flushing the nozzle, is dispensed before each dose is dispensed.

16 Claims, 3 Drawing Sheets



(56) **References Cited**

U.S. PATENT DOCUMENTS

6,578,741	B2 *	6/2003	Ritsche et al.	222/153.13
6,890,517	B2 *	5/2005	Drechsel et al.	424/45
2003/0145849	A1 *	8/2003	Drinan et al.	128/200.14
2004/0015126	A1 *	1/2004	Zierenberg et al.	604/72
2005/0061314	A1 *	3/2005	Davies et al.	128/200.23
2005/0098172	A1 *	5/2005	Anderson	128/200.23
2005/0183718	A1	8/2005	Wuttke et al.	
2006/0285987	A1	12/2006	Jaeger	
2008/0092885	A1 *	4/2008	von Schuckmann	128/203.15

FOREIGN PATENT DOCUMENTS

EP	1003478	A1	5/2000
JP	2004097617	A *	4/2004
WO	9114468	A1	10/1991
WO	9606011	A2	2/1996
WO	9712687	A1	4/1997
WO	98/12511	A2	3/1998

* cited by examiner

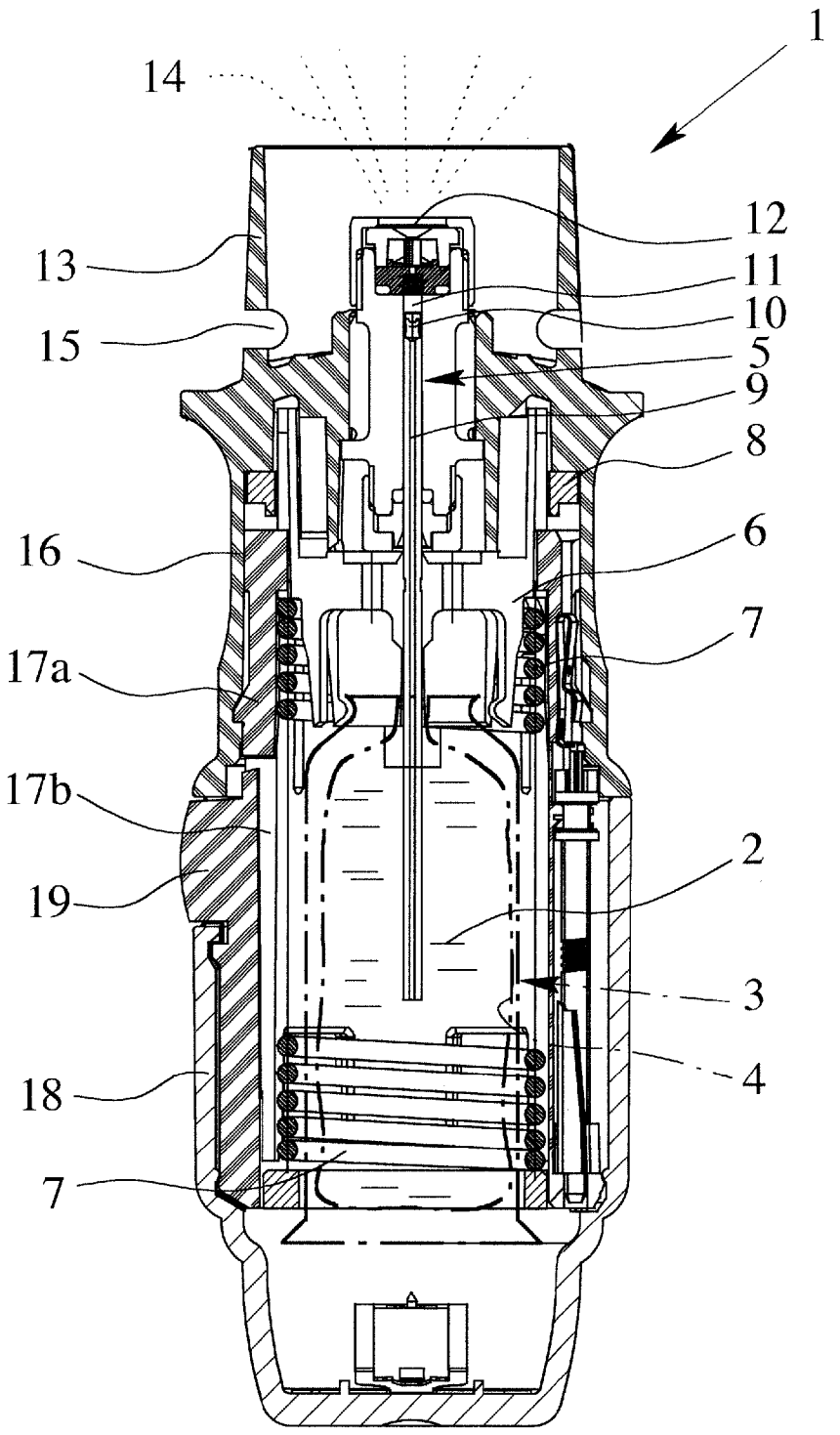


Fig. 1

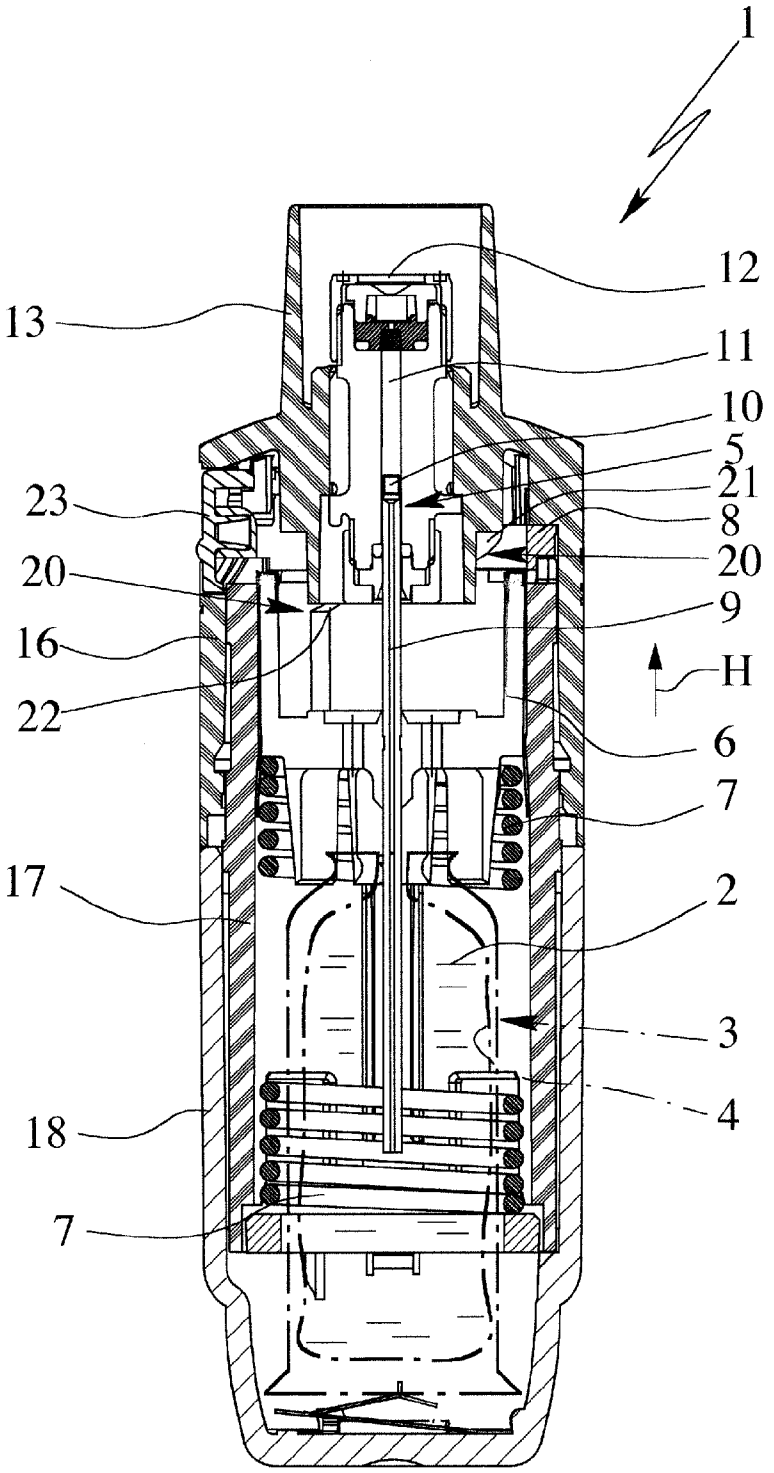


Fig. 2

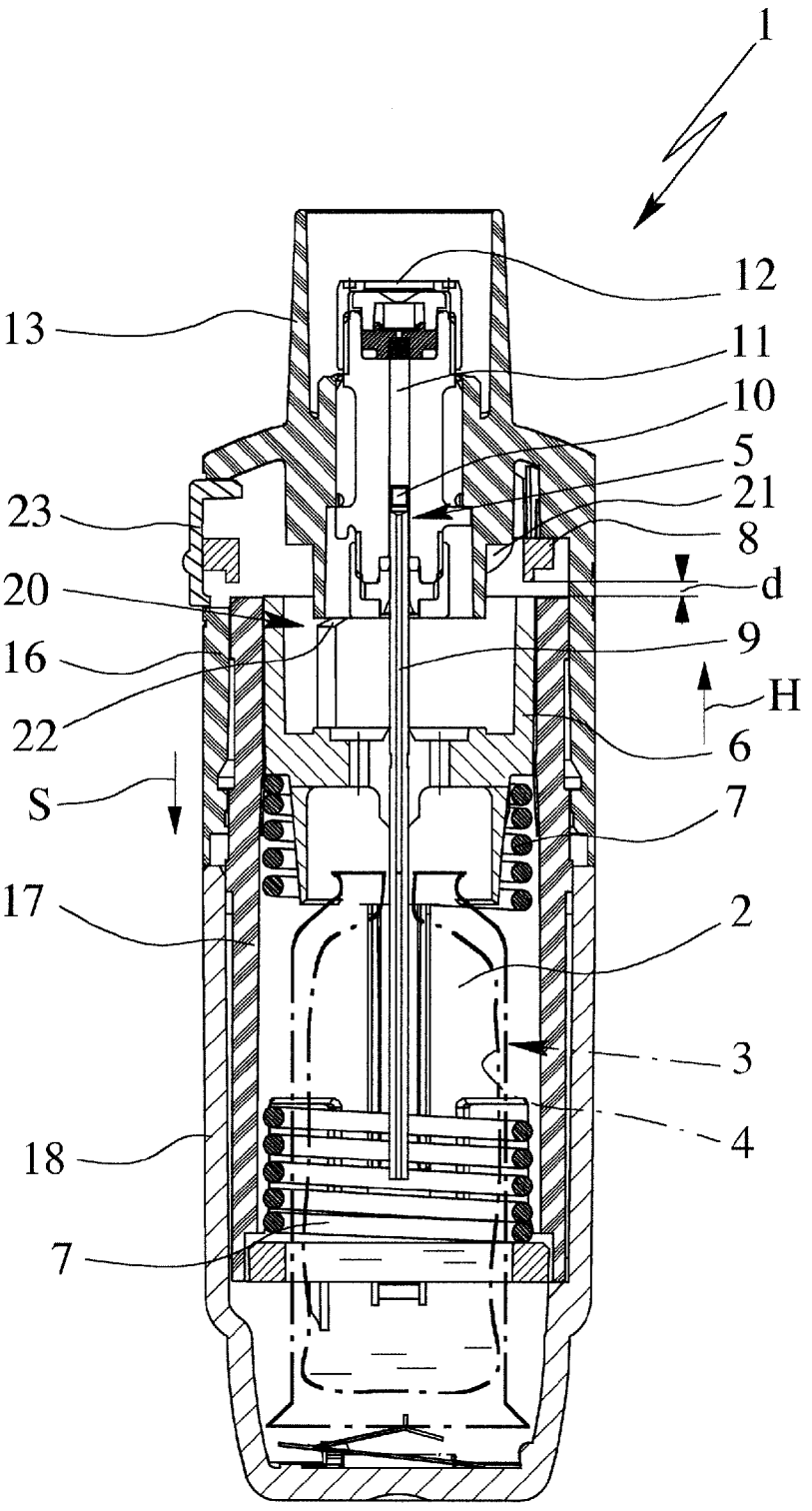


Fig. 3

ATOMIZER AND METHOD OF ATOMIZING FLUID WITH A NOZZLE RINSING MECHANISM

This application is the national phase entry under 35 U.S.C. §371 of International Application No. PCT/EP2007/003322, filed Apr. 16, 2007, which claims priority to German Application No. DE 10 2006 022 002.1, filed May 10, 2006, each of which is hereby incorporated by reference in its entirety.

BACKGROUND

1. Field of the Invention

The present invention relates to an atomizer according to the preamble of claim **1**, a process according to the preamble of claim **12** and a use of the atomizer.

2. Related Art

An atomizer is known under the brand name "Respimat" in the form of an inhaler as disclosed in general terms in WO 91/14468 A1 and specifically illustrated in WO 97/12687 A1 (FIG. 6*a*, 6*b*). The atomizer has, as a reservoir for a fluid which is to be atomised, an insertable container, a pressure generator with a drive spring and a nozzle through which the fluid is expelled and atomised.

After the container is used for the first time or left unused for any length of time, air in the pressure generator or nozzle system may cause the metering accuracy to be negatively affected when fluid is next expelled and atomised. This is not the case during the subsequent expulsion and atomisation, as any air present has been displaced by the fluid. Before the atomizer is used for the first time and after lengthy periods of non-use, it is therefore recommended that at least one dose of fluid should be expelled without being inhaled. This preliminary actuation is also referred to as "priming". Priming leads to an increased consumption of fluid and requires special care on the part of the user.

SUMMARY OF THE INVENTION

The aim of the present invention is to provide an atomizer and a process and a use of such an atomizer, such that particularly accurate metering is possible by simple means and with easy operation, and in particular so that there is no need for any priming.

This aim is achieved by an atomizer as disclosed and described herein.

A fundamental idea of the present invention is that in each case a preliminary amount of fluid, which is very small in relation to the dose, for rinsing the nozzle and any other delivery means of the atomizer in question, should be expelled preferably automatically before each intended delivery of a dose or each time the atomizer is tensioned. The term "intended" makes it clear that during the very first priming, the so-called dry priming, of the atomizer there is no intention of delivering a dose, nor is any dose delivered, and also no preliminary amount is expelled, in particular when initially only air is forced out of the conveying system of the atomizer. The delivery or production of the pre-spray has a number of advantages.

Rinsing with the preliminary amount can further improve the metering accuracy of the atomizer.

The air and other gases contained in the pressure generator or the like are displaced or at least substantially reduced by the preliminary amount. This improves the dosing accuracy during the next delivery.

The preliminary amount makes it possible for example to achieve a definite closure or other assumption of a defined position of a valve, particularly of the pressure generator, so that more defined states can be achieved during the actual use of the atomizer and dosing of the fluid intended for inhalation, in particular.

Moreover, thanks to the preliminary amount a defined break-off of fluid at the nozzle can be achieved, which corresponds substantially to that which occurs during the expulsion of fluid that takes place immediately after, as a result of which again the metering accuracy is further improved.

The rinsing of the nozzle by the preliminary amount can eliminate or detach deposits, contamination or microbial impurities.

Increases in concentration—e.g. as a result of evaporation during non-use—can also be reduced or prevented.

In the present invention, the term "rinsing the nozzle" preferably relates not only to the nozzle or nozzle system of the atomizer, but alternatively or additionally also relates to the pressure generator or other parts of the atomizer for conveying, expelling and atomising fluid, such as any filter, pressure chamber, valve, intake line, pressure line or the like which may be provided.

If oligodynamic silver compounds or other ion-releasing compounds are used in the atomizer, the silver ions or other ions may be expelled by the preliminary amount so that fewer ions are expelled and inhaled during actual use.

The proposed rinsing by the preliminary amount preferably occurs automatically, i.e. without separate operation or actuation by the user, particularly each time the atomizer or any spring contained therein is put under tension. Accordingly, very simple operation is achieved. Particularly preferably, the above-mentioned priming can be omitted altogether or at least reduced.

It has been found that a surprisingly small preliminary amount is sufficient in particular to achieve the advantages mentioned above. Even if the nozzle is rinsed with the preliminary amount on every actuation or use of the atomizer, the prospective overall fluid consumption is less, as priming leads to the expulsion of a full dose of fluid, even if it is not carried out before every use of the atomizer.

The preliminary amount of fluid is delivered as a spray mist and/or as drops, depending in particular on the pressure through the nozzle. The rinsing of the nozzle by the preliminary amount and its delivery through the nozzle—irrespective of whether it is in the form of a spray mist or drops—is also referred to as "pre-spray".

Further advantages, features, properties and aspects of the present invention will become apparent from the claims and the following description of a preferred embodiment by reference to the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic section through an atomizer in the non-tensioned state;

FIG. **2** is a schematic section through the atomizer in the tensioned state after rotation through 90° relative to FIG. **1**;

FIG. **3** is a schematic section through an atomizer with additional functionality.

In the Figures the same reference numerals have been used for identical or similar parts, and corresponding or comparable properties and advantages are achieved even if the associated description is not repeated.

DETAILED DESCRIPTION OF THE INVENTION

FIGS. **1** and **2** show an atomizer **1** for atomising a fluid **2**, particularly a highly effective medicament or the like, shown

schematically in the non-tensioned state (FIG. **1**) and in the tensioned state (FIG. **2**). The atomizer **1** is embodied in particular as a portable inhaler and preferably operates without propellant gas.

Atomisation of the fluid **2**, preferably a liquid, more particularly a medicament, produces an aerosol which can be breathed in or inhaled by a user (not shown). Normally, the medicament is inhaled at least once a day, more particularly several times a day, preferably at predetermined intervals, depending on the ailment affecting the patient.

The atomizer **1** has a preferably insertable and preferably replaceable container **3** containing the fluid **2**. The container **3** thus forms a reservoir for the fluid **2** which is to be atomised, which is held in particular in a fluid chamber **4** formed by a collapsible bag in the container **3**.

Preferably, the container **3** contains a sufficient amount of fluid **2** or active substance to provide, for example, up to 200 dosage units or doses, i.e. to allow up to 200 sprays or applications. A typical container **3** as disclosed in WO 96/06011 A2 holds a volume of about 2 to 10 ml.

The atomizer **1** also comprises a pressure generator **5** for delivering and atomising the fluid **2**, particularly in a predetermined or adjustable dosage amount. The fluid **2** can thus be expelled and atomised in individual doses, particularly from about 5 to 30 μl.

The pressure generator **5** has a holder **6** for the container **3**, an associated drive spring **7** which is only partly shown, a locking element **8** which is preferably manually operable to release it, a movable conveying element, particularly a conveying tube **9**, a non-return valve **10**, a pressure chamber **11** and a nozzle **12** in the region of a mouthpiece **13**. The container **3** is fixed, particularly by latching, in the atomizer **1** via the holder **6** such that the conveying tube **9** dips into the container **3**. The holder **6** may be embodied such that the container **3** can be detached and replaced.

For axially tensioning the drive spring **7**, the holder **6** with the container **3** and the conveying tube **9** is moved downwards in the drawings and fluid **2** is sucked out of the container **3** through the non-return valve **10** into the pressure chamber **11** of the pressure generator **5**.

During the subsequent release of tension after actuation of the locking element **8** to release the holder **6**, the fluid **2** in the pressure chamber **11** is put under pressure by moving the conveying tube **9** with its now closed non-return valve **10** back upwards, by releasing the drive spring **7** (main movement), i.e. to act as a ram. This pressure expels the fluid **2** through the nozzle **12**, during which time it is atomised into an aerosol **14**, as indicated in FIG. **1**.

A user or patient (not shown) can inhale the aerosol **14**, while a supply of air can be sucked into the mouthpiece **13** through at least one air inlet opening **15**.

The atomizer **1** has an upper housing part **16** and an inner part **17** which is rotatable relative thereto (FIG. **2**) having an upper part **17***a* and a lower part **17***b* (FIG. **1**), while an in particular manually operable housing part **18** is releasably attached to, in particular pushed onto, the inner part **17**, preferably by means of a holding element **19**. For inserting and/or changing the container **3**, the housing part **18** can be detached from the atomizer **1**.

The housing part **18** can be rotated relative to the upper housing part **16**, carrying the inner part **17** with it. The upper part **17***a* rotates the holder **6** by corresponding engagement therewith, so that this holder is axially moved counter to the force of the drive spring **7** by means of a gear **20** which is merely indicated in FIG. **2** and the drive spring **7** is tensioned.

During tensioning, the container **3** is moved axially downwards. Finally, the container **3** assumes an end position as shown in FIG. **2**. In this end position, the drive spring **7** is under tension. The locking element **8** can then secure the holder **6** and hence the conveying tube **9** and the container **3** against movement in the upward direction in the Figure, i.e. prevent the drive spring **7** from relaxing. In the view shown in FIG. **2** the holder **6** together with the conveying tube **9** and the container **3** and the drive spring **7** are in the tensioned state or in the tensioning position, but the locking element **8** is not in its transversely or radially shifted locking position that blocks the holder **6**.

After the holder **6** has been released by the locking element **8**—i.e. starting from the clamping position shown in FIG. **2** and in the position of the locking element **8** shown in FIG. **2**—the atomising process takes place. The holder **6** together with the conveying tube **9** and the container **3** is returned to the starting position shown in FIG. **1** by the force of the drive spring **7**. This movement is also referred to hereinafter as the main movement H, for short. During the main movement, the valve **10** is closed and the conveying tube **9** puts the fluid **2** contained in the pressure chamber **11** under pressure, so that this fluid is expelled through the nozzle **12** and atomised.

The container **3** thus preferably performs a lifting movement during the clamping process or for the withdrawal of fluid and during the atomising process.

In the embodiment shown the gear **20** for clamping the atomizer **1** or drive spring **7** and for axially moving the holder **6** in the tensioning direction preferably has sliding surfaces **21** and **22** on the upper housing part **18** and/or on the holder **6**, which extend in particular in a helical configuration and lead to the desired axial movement of the holder **6** when the holder **6** is rotated relative to the upper housing part **16**.

When the holder **6** reaches the clamping position shown in FIG. **2**, the sliding surfaces **21**, **22** move out of engagement, and the gear **20** releases the holder **6** for the opposite movement in the axial direction, particularly the main movement. At the same time, the locking element **8** is shifted into its locking position (shown in FIG. **3**) transversely, particularly radially, to the axial movement or axial direction, such that the holder **6** and hence the conveying tube **9** and container **3** are blocked or secured in the tensioning position. In particular the locking element **8** is of annular construction and in its locking position is radially shifted out of the normally concentric arrangement with the holder **6**, so that the holder **6** abuts with its end face on a portion of the locking element **8** and is blocked thereby.

To initiate the atomising process, the locking element **8** which is provided in particular with a button **23** or other actuating element is actuated and thereby moved back radially into its concentric position as shown in FIG. **2**, as a result of which the blocking of the holder **6** is cancelled and the holder is able to perform the main movement in the direction of the arrow H. Any fluid **2** then contained in the pressure chamber **11** is expelled through the nozzle **12** and atomised.

The structure and mode of operation of a proposed atomizer are hereinafter explained by reference to the schematic sectional view in FIG. **3**, which is not to scale and which substantially corresponds to the view in FIG. **2**. The earlier remarks particularly relating to FIGS. **1** and **2** still apply or have a complementary value.

The proposed atomizer **1** is constructed so that before each delivery and atomisation of a dose of fluid **2** a specific preliminary amount of fluid **2** is expelled. This preliminary amount rinses the nozzle **12** or other conveying means, components or the like of the atomizer **1**, particularly the conveying tube **9**, the valve **10**, the pressure chamber **11**, a channel leading to the nozzle **12**, an optional filter in front of the nozzle **12**, the nozzle **12** or the like. The rinsing with the

preliminary amount takes place in particular automatically on each actuation of the atomizer **1**, particularly on each tensioning of the atomizer **1**, and results in the pre-spray and the advantages described above.

The preliminary amount is preferably very small, but requires a certain minimum amount in order to achieve the desired advantages. It is preferably at least 0.5 µl, particularly 0.5 to 3 µl, most preferably about 1 to 2 µl. This is very little compared with the usual dose of fluid **2** (in particular about 15 to 20 µl), which is delivered on each atomisation. Preferably, the preliminary amount is at least 1%, more particularly at least 2%, most preferably about 3 to 10%, of the amount of a dose of the fluid **2** delivered during a normal atomisation process.

Particularly preferably, the preliminary amount is at least five times the volume of the nozzle **12** or of a nozzle block forming the nozzle **12**. This of itself guarantees effective rinsing of the nozzle **12**.

The following is an explanation of how the preliminary amount and the rinsing with the preliminary amount of fluid **2** are obtained.

During the tensioning of the atomizer **1** or the drive spring **7** in the tensioning direction S, the holder **6** and hence the conveying element **9** is moved into an over-tensioning position as shown in FIG. **3**. In this over-tensioning position, the gear **20** releases the holder **6**, so that an opposite movement can then take place as a result of the spring force, as in the normal atomisation process. The present invention envisages that a first movement—hereinafter referred to as the preliminary movement—takes place in this direction H, but initially only until the (normal) tensioning position is reached, i.e. until the holder **6** comes to abut on the locking element **8** which is in the locking position, in the embodiment shown. FIG. **3** shows the locking element **8** in the locking position with the button **23** extended. FIG. **2** shows the locking element **8** in the non-locking position, i.e. in the position in which the holder **6** is not blocked, with the button **23** pushed in, or in a concentric position.

The holder **6** and hence also the conveying element or conveying tube **9** automatically perform the preliminary movement into the tensioning position, from the over-tensioning position shown in FIG. **3**, i.e. until blocked by the locking element **8**. This preliminary movement, which preferably takes place in the same direction as the main movement H mentioned earlier during the normal atomising process, leads to the production and delivery of the desired preliminary amount of fluid **2**.

The preliminary movement is very short by comparison with the main movement. In particular its stroke d, i.e. the distance from the over-tensioning position into the tensioning position, is only about 0.2 to 1 mm, in particular about 0.4 to 0.8 mm.

If required, the stroke d may be adjusted or fixed to adapt to the nozzle **12**, the pressure generator **5** or the like and/or to adapt to the particular fluid **2**. The volume of the preliminary amount can be varied accordingly by varying the stroke d.

Depending on the volume of the preliminary amount and the pressure increase—particularly the speed of return of the conveying element or conveying tube **9** from the over-tensioning position into the clamping position—and depending on the fluid **2**, the preliminary amount is expelled in the form of drops and/or as a spray mist or spray jet. The user can if necessary wipe or shake off the drop and optionally other residual amounts of fluid **2** remaining on the nozzle **12** during normal use of the atomizer **1**. Alternatively or additionally, the drop or the residual amounts can also be wiped away or absorbed by means of a covering cap (not shown) for closing off the mouthpiece **13**, particularly a wiper or absorption means, such as a piece of non-woven fabric or the like, accommodated in the covering cap.

The covering cap may be of transparent construction, at least in parts, so that the user can monitor the expulsion of the preliminary amount. Alternatively, it is also possible that the user will not monitor the expulsion of the preliminary amount and in particular will not notice it either. In fact, the expulsion of the preliminary amount may take place almost imperceptibly and so fast that it does not interfere with the normal handling and use of the atomizer **1** for delivering and atomising fluid **2**.

According to a further feature (not shown) an additional barrier or delay may be provided, so that the tensioned atomizer **1**—i.e. the tensioning element **8** or the button **23** in this embodiment—can only be actuated when the preliminary amount of fluid **2** has been expelled or the holder **6** and the conveying tube **9** have reached the tensioning position, i.e. the holder **6** is abutting on the locking element **8**. This is a way of preventing the preliminary amount from being expelled and atomised together with the actual dose of fluid **2**, i.e. so that the normal dose is undesirably increased by the preliminary amount.

After the preliminary amount has been expelled, the user can operate the atomizer **1** completely normally, in particular by pressing the button **23** to move the locking element **8** out of the locking position into the position, which is concentric in this embodiment, which does not block the holder **6**. Thus the holder **6** is freed and normal delivery and atomisation take place. As a result of the spring force of the drive spring **7** the conveying tube **9** performs the main movement H, while any fluid **2** contained in the pressure chamber **11** is expelled and atomised through the nozzle **12**.

Surprisingly, it was found that the deliberately selected preliminary amount can be used to rinse the nozzle **12** or the entire nozzle or delivery system, in particular in order to expel or detach any deposits, dirt or microbial contamination immediately before using the atomizer **1**, i.e. immediately before inhalation, in particular. The proposed rinsing with the preliminary amount also decreases the risk of blockage of the nozzles caused by deposits, contamination, crystallisation or the like.

In addition, undesirable increases in concentration, particularly in the nozzle region, can be avoided or at least minimised. Such concentrations—e.g. an undesirable increase in an active substance or other material—occur particularly with fluids **2** that contain solvent, particularly ethanolic or ethanol-containing fluids **2**. The prevention or reduction of concentrations in the nozzle region also helps to ensure greater metering accuracy.

The metering accuracy can also be further improved by the fact that the preliminary amount moistens parts of the pressure generator **5** or nozzle system before they are actually used.

A particular advantage of the proposed rinsing with the preliminary amount is that it occurs on each actuation, particularly each tensioning, of the atomizer **1**—i.e. in particular automatically—and cannot or need not be influenced by the user.

The proposed rinsing can also be used to improve the microbiological condition of the inhaler still further. In particular, any pathogens formed are expelled. If oligodynamic silver compounds are used in the atomizer **1**, any silver ions produced are expelled by the rinsing with the preliminary amount, so that fewer silver ions are delivered and inhaled.

The proposed rinsing with the preliminary amount also causes the valve **10** to be moved into a defined closed position,

so that during the subsequent actual operation of the atomizer **1**, the fluid **2** is immediately put under pressure and expelled. The closure time of the valve **10** is in fact reduced and stabilised. As a result the variability of the volume delivered is reduced, i.e. a further improvement in the metering accuracy can be obtained.

The above-mentioned effects and advantages can be obtained with a surprisingly small preliminary amount, in particular with the volumes or ratios mentioned hereinbefore.

It should be noted that the proposed rinsing before the actual delivery of the fluid can generally be implemented in other atomizers as well. In particular other constructional solutions and alternatives to the proposed rinsing or production of the preliminary amount can also be used. Different constructional solutions to the locking and unlocking in the tensioning position are also possible. Generally, instead of the drive spring **7** it is also possible to use a different spring or drive means. Even if the conveying element is manually driven in the main direction or direction of delivery, it is possible to produce and expel the preliminary amount for rinsing purposes.

In contrast to freestanding apparatus or the like, the proposed atomizer **1** is preferably designed to be portable and in particular it is a mobile hand-held device.

However, the proposed solution may be used not only in the atomizers **1** that are specifically described here but also in other atomizers or inhalers, e.g. powder inhalers or so-called "metered dose inhalers".

The atomizer **1** is particularly preferably embodied as an inhaler, particularly for medicinal aerosol therapy. Alternatively, however, the atomizer **1** can also be designed for other uses, preferably for atomising a cosmetic liquid and particularly as a perfume atomizer. The container **3** correspondingly contains, for example, a medicament formulation or a cosmetic liquid such as perfume or the like.

Preferably, the fluid **2** is a liquid as already mentioned, in particular an aqueous or ethanolic medicament formulation. However, it may also be some other medicament formulation, a suspension or the like or particles or powder.

Some preferred ingredients and/or formulations of the preferably medicinal fluid **2** are listed below. As already mentioned, they may be aqueous or non-aqueous solutions, mixtures, ethanol-containing or solvent-free formulations. Particularly preferably, the fluid **2** contains:

The compounds listed below may be used in the device according to the invention on their own or in combination. In the compounds mentioned below, W is a pharmacologically active substance and is selected (for example) from among the betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists and PI3-kinase inhibitors. Moreover, double or triple combinations of W may be combined and used in the device according to the invention. Combinations of W might be, for example:

- W denotes a betamimetic, combined with an anticholinergic, corticosteroid, PDE4-inhibitor, EGFR-inhibitor or LTD4-antagonist,
- W denotes an anticholinergic, combined with a betamimetic, corticosteroid, PDE4-inhibitor, EGFR-inhibitor or LTD4-antagonist,
- W denotes a corticosteroid, combined with a PDE4-inhibitor, EGFR-inhibitor or LTD4-antagonist
- W denotes a PDE4-inhibitor, combined with an EGFR-inhibitor or LTD4-antagonist
- W denotes an EGFR-inhibitor, combined with an LTD4-antagonist.

The compounds used as betamimetics are preferably compounds selected from among albuterol, arformoterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmefamol, salmeterol, soterenol, sulphonterol, terbutaline, tiaramide, tolubuterol, zinterol, CHF-1035, HOKU-81, KUL-1248 and

3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzyl-sulphonamide
5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one
4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl] sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone
1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol
1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol
1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino] ethanol
1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol
1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol
1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol
5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one
1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol
6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one
6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1.1 dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one
8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one
4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid
8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one
1-(4-ethoxy-carbonylamino-3-cyano-5-fluorophenyl)-2-(tert-butylamino)ethanol
2-hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-benzaldehyde
N-[2-hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-phenyl]-formamide
8-hydroxy-5-(1-hydroxy-2-{2-[4-(6-methoxy-biphenyl-3-ylamino)-phenyl]-ethylamino}-ethyl)-1H-quinolin-2-one
8-hydroxy-5-[1-hydroxy-2-(6-phenethylamino-hexylamino)-ethyl]-1H-quinolin-2-one

5-[2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one

[3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-5-methyl-phenyl]-urea

4-(2-{6-[2-(2,6-dichloro-benzyloxy)-ethoxy]-hexylamino}-1-hydroxy-ethyl)-2-hydroxymethyl-phenol

3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzylsulphonamide

3-(3-{7-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-heptyloxy}-propyl)-benzylsulphonamide

4-(2-{6-[4-(3-cyclopentanesulphonyl-phenyl)-butoxy]-hexylamino}-1-hydroxy-ethyl)-2-hydroxymethyl-phenol

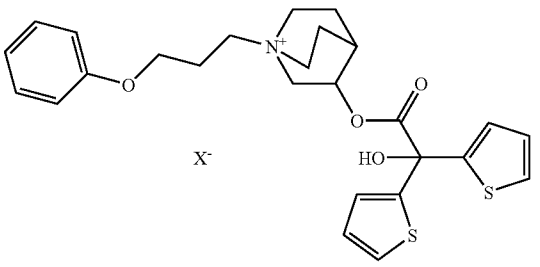
N-adamantan-2-yl-2-(3-{2-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl}-phenyl)-acetamide

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

The anticholinergics used are preferably compounds selected from among the tiotropium salts, preferably the bromide salt, oxitropium salts, preferably the bromide salt, flutropium salts, preferably the bromide salt, ipratropium salts, preferably the bromide salt, glycopyrronium salts, preferably the bromide salt, trospium salts, preferably the chloride salt, tolterodine. In the above-mentioned salts the cations are the pharmacologically active constituents. As anions the above-mentioned salts may preferably contain the chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate, while chloride, bromide, iodide, sulphate, methanesulphonate or p-toluenesulphonate are preferred as counter-ions. Of all the salts the chlorides, bromides, iodides and methanesulphonates are particularly preferred.

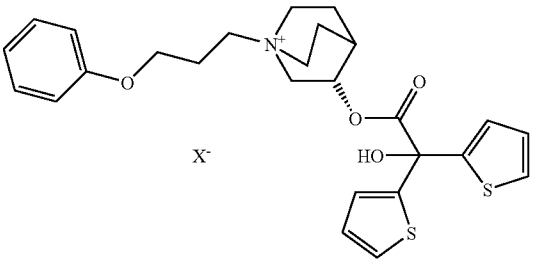
Other preferred anticholinergics are selected from among the salts of formula AC-1

AC-1



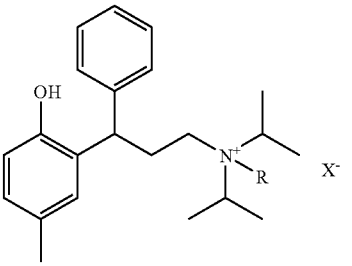
wherein X^- denotes an anion with a single negative charge, preferably an anion selected from among the fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate, preferably an anion with a single negative charge, particularly preferably an anion selected from among the fluoride, chloride, bromide, methanesulphonate and p-toluenesulphonate, particularly preferably bromide, optionally in the form of the racemates, enantiomers or hydrates thereof. Of particular importance are those pharmaceutical combinations which contain the enantiomers of formula AC-1-en

AC-1-en



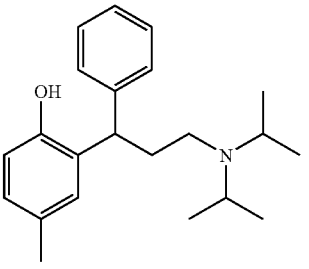
wherein X^- may have the above-mentioned meanings. Other preferred anticholinergics are selected from the salts of formula AC-2

AC-2



wherein R denotes either methyl or ethyl and wherein X^- may have the above-mentioned meanings. In an alternative embodiment the compound of formula AC-2 may also be present in the form of the free base AC-2-base.

AC-2-base



Other specified compounds are:
tropenol 2,2-diphenylpropionate methobromide,
scopine 2,2-diphenylpropionate methobromide,
scopine 2-fluoro-2,2-diphenylacetate methobromide,
tropenol 2-fluoro-2,2-diphenylacetate methobromide;
tropenol 3,3',4,4'-tetrafluorobenzilate methobromide,
scopine 3,3',4,4'-tetrafluorobenzilate methobromide,
tropenol 4,4'-difluorobenzilate methobromide,
scopine 4,4'-difluorobenzilate methobromide,
tropenol 3,3'-difluorobenzilate methobromide,
scopine 3,3'-difluorobenzilate methobromide;

tropenol 9-hydroxy-fluorene-9-carboxylate methobromide;
tropenol 9-fluoro-fluorene-9-carboxylate methobromide;
scopine 9-hydroxy-fluorene-9-carboxylate methobromide;
scopine 9-fluoro-fluorene-9-carboxylate methobromide;
tropenol 9-methyl-fluorene-9-carboxylate methobromide;
scopine 9-methyl-fluorene-9-carboxylate methobromide;
cyclopropyltropine benzilate methobromide;
cyclopropyltropine 2,2-diphenylpropionate methobromide;
cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide;
cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide;
cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide;
cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide;
cyclopropyltropine methyl 4,4'-difluorobenzilate methobromide.
tropenol 9-hydroxy-xanthene-9-carboxylate methobromide;
scopine 9-hydroxy-xanthene-9-carboxylate methobromide;
tropenol 9-methyl-xanthene-9-carboxylate methobromide;
scopine 9-methyl-xanthene-9-carboxylate methobromide;
tropenol 9-ethyl-xanthene-9-carboxylate methobromide;
tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide;
scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide,

The above-mentioned compounds may also be used as salts within the scope of the pre-sent invention, wherein instead of the methobromide the salts metho-X are used, wherein X may have the meanings given hereinbefore for X^-.

As corticosteroids it is preferable to use compounds selected from among beclomethasone, betamethasone, budesonide, butixocort, ciclesonide, deflazacort, dexamethasone, etiprednol, flunisolide, fluticasone, loteprednol, mometasone, prednisolone, prednisone, rofleponide, triamcinolone, RPR-106541, NS-126, ST-26 and
(S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate
(S)-(2-oxo-tetrahydro-furan-3 S-yl)6,9-difluoro-1,1-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate,
cyanomethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tertamethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylate
optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof. Any reference to steroids includes a reference to any salts or derivatives, hydrates or solvates thereof which may exist. Examples of possible salts and derivatives of the steroids may be: alkali metal salts, such as for example sodium or potassium salts, sulphobenzoates, phosphates, isonicotinates, acetates, dichloroacetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

PDE4-inhibitors which may be used are preferably compounds selected from among enprofyllin, theophyllin, roflumilast, ariflo (cilomilast), tofimilast, pumafentrin, lirimilast, arofyllin, atizoram, D-4418, Bay-198004, BY343, CP-325.366, D-4396 (Sch-351591), AWD-12-281 (GW-842470), NCS-613, CDP-840, D-4418, PD-168787, T-440, T-2585, V-11294A, Cl-1018, CDC-801, CDC-3052, D-22888, YM-58997, Z-15370 and
N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide
(−)p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[s][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide
(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone
3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone
cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]
2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)cyclohexan-1-one
cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]
(R)-(+)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate
(S)-(−)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate
9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine
9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine
optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

The LTD4-antagonists used are preferably compounds selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707, L-733321 and
1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetic acid,
1-(((1(R)-3 (3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetic acid
[2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid
optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate. By salts or derivatives which the LTD4-antagonists may optionally be capable of forming are meant, for example: alkali metal salts, such as for example sodium or potassium salts, alkaline earth metal salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

EGFR-inhibitors which may be used are preferably compounds selected from among cetuximab, trastuzumab, ABX-EGF, Mab ICR-62 and
4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]-amino}-7-cyclopropylmethoxy-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline

4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-to-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropy-lmethoxy-quinazoline

4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline

4-[(3-ethynyl-phenyl)amino]-6,7-to-(2-methoxy-ethoxy)-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinyl-carbonyl)amino]-quinazoline

4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline

4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl) quinazoline

4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]-amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-to-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline

4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydro furan-2-yl)methoxy]-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxy-carbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonyl-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline
4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline
4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline
4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline
4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline
4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline
4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline
4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxy-ethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydro furan-2-yl)methoxy]-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

The dopamine agonists used are preferably compounds selected from among bromocriptin, cabergoline, alpha-dihydroergocryptine, lisuride, pergolide, pramipexol, roxindol, ropinirol, talipexol, tergurid and viozan, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

H1-Antihistamines which may be used are preferably compounds selected from among epinastine, cetirizine, azelastine, fexofenadine, levocabastine, loratadine, mizolastine,

ketotifen, emedastine, dimetindene, clemastine, bamipine, cexchlorpheniramine, pheniramine, doxylamine, chlorophenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastine, desloratidine and meclozine, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

It is also possible to use inhalable macromolecules as disclosed in EP 1 003 478 A1 or CA 2297174 A1.

In addition, the compound may come from the groups of ergot alkaloid derivatives, the triptans, the CGRP-inhibitors, the phosphodiesterase-V inhibitors, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates and/or hydrates thereof.

Examples of ergot alkaloid derivatives are dihydroergotamine and ergotamine.

LIST OF REFERENCE NUMERALS

1 atomizer
2 fluid
3 container
4 fluid chamber
5 pressure generator
6 holder
7 drive spring
8 locking element
9 conveying tube
10 non-return valve
11 pressure chamber
12 nozzle
13 mouthpiece
14 aerosol
15 air inlet opening
16 upper housing part
17 inner part
17*a* upper part of the inner part
17*b* lower part of the inner part
18 housing part (lower part)
19 holding element
20 gear
21 sliding surface
22 sliding surface
23 button
H main movement
S tensioning movement
d stroke

The invention claimed is:

1. An atomizer (**1**) for a fluid (**2**), comprising:
a fluid reservoir in the form of a container (**3**);
a nozzle (**12**) for the delivery and atomization of the fluid (**2**), wherein the fluid (**2**) is delivered in metered individual full-doses; and
a conveying element in the form of a conveying tube (**9**), which is movable for conveying the fluid, which is movable: (i) in a preliminary movement to a tensioning position for delivering a preliminary amount of the fluid, and thereafter (ii) in a main movement for delivering a full-dose for actual delivery and atomization of the fluid (**2**),
wherein the conveying element is movable counter to a spring force by at least one of: (i) a gear (**20**), and (ii) manual actuation of the atomizer (**1**) into an over-tensioning position from which the conveying element is moved by spring force into the tensioning position,
wherein the preliminary amount of fluid (**2**), which is substantially less than a metered individual full-dose, rinses the nozzle (**12**) and is delivered before delivery of each metered individual full-dose or on each tensioning of the atomizer (**1**).

2. The atomizer according to claim **1**, wherein the preliminary amount is between 0.5 to 3.0 microliters.

3. The atomizer according to claim l, wherein the preliminary amount is one of: (i) between 1 to 10 percent of an amount of each full-dose and (ii) at least five times a volume of the nozzle (**12**).

4. The atomizer according to claim **1**, wherein the preliminary movement and main movement are carried out exclusively by spring force.

5. The atomizer according to claim **1**, wherein a stroke (d) of the preliminary movement is 0.2 to 1 millimeters.

6. The atomizer according to claim **1**, wherein the atomizer (**1**) has a locking element (**8**) which in a locking position secures the conveying element directly or indirectly in the tensioning position and can be moved manually out of the locking position in order to release the conveying element.

7. The atomizer according to claim **1**, wherein the atomizer (**1**) contains a fluid (**2**) that contains a solvent.

8. The atomizer according to claim **1**, wherein the atomizer (**1**) contains an inhalable formulation or a medicament in the form of a fluid (**2**), selected from anticholinergics, betamimetics, steroids, phosphodiesterase IV-inhibitors, LTD4-antagonists and EGFR-kinase-inhibitors, antiallergics, ergot alkaloid derivatives, triptans, CGRP-antagonists, phosphodiesterase-V-inhibitors, and any combination of each of the foregoing.

9. The atomizer according to claim **1**, wherein the atomizer (**1**) is constructed as a portable inhaler for medicinal aerosol therapy.

10. The atomizer according to claim **1**, wherein the fluid includes a medicament selected from anticholinergics, betamimetics, steroids, phosphodiesterase IV-inhibitors, LTD4-antagonists and EGFR-kinase-inhibitors, antiallergics, ergot alkaloid derivatives, triptans, CGRP-antagonists, phosphodiesterase-V-inhibitors, and any combination of each of the foregoing.

11. A method for delivering and atomizing fluid (**2**), which is delivered in individual, metered full-doses through a nozzle (**12**), the method comprising:
moving a conveying element in the form of a conveying tube (**9**) for conveying the fluid in a preliminary movement to a tensioning position for delivering a preliminary amount of the fluid; and
thereafter moving the conveying element in a main movement for delivering an individual metered full-dose for actual delivery and atomization of the fluid (**2**), wherein the conveying element is movable counter to a spring force into an over-tensioning position, and from which the conveying element is moved by spring force into the tensioning position, and
wherein the preliminary amount of fluid (**2**) is substantially less than the individual metered full-dose, and rinses the nozzle (**12**) before delivery of each individual metered full-dose or on each tensioning of the atomizer (**1**).

12. The method according to claim **11**, wherein the preliminary amount is between 0.5 and 3.0 microliters.

13. The method according to claim **11**, wherein the preliminary amount is between 1 to 10 percent of the amount of the full-dose.

14. The method according to claim **11**, wherein the preliminary movement and main movement are carried out exclusively by spring force.

15. The method according to claim **11**, wherein a stroke (d) of the preliminary movement is 0.2 to 1 millimeters.

16. The method according to claim **11**, wherein the conveying element is released in the tensioning position by manual operation of a locking element (**8**).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,733,341 B2
APPLICATION NO. : 12/299650
DATED : May 27, 2014
INVENTOR(S) : Boeck et al.

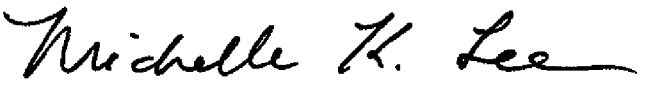
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1279 days.

Signed and Sealed this
Twenty-fifth Day of August, 2015



Michelle K. Lee
Director of the United States Patent and Trademark Office