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., Boehringer Ingelheim International GmbH, and Boehringer Ingelheim Pharma GmbH & Co. KG

Of Counsel:

Christopher N. Sipes
R. Jason Fowler
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., BOEHRINGER INGELHEIM INTERNATIONAL GMBH, and BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, **Plaintiffs,** **v.** **ALVOGEN, INC.,** **Defendant.**	**Civil Action No. _____** **(Filed Electronically)**

COMPLAINT FOR PATENT INFRINGEMENT

Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH, and Boehringer Ingelheim Pharma GmbH & Co. KG (collectively, "Boehringer"), by their undersigned attorneys, bring this action against Alvogen, Inc. ("Alvogen"), 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 Alvogen's submission of Abbreviated New Drug Application No. 211704 to the United States Food and Drug Administration (FDA). Through this ANDA, Alvogen seeks approval to market a generic version of the pharmaceutical product SPIRIVA® HandiHaler® prior to the expiration of United States Patent No. 9,010,323 ("the '323 patent" or "patent-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. §§ 2201–02 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. Boehringer Ingelheim Pharma GmbH & Co. KG is a corporation organized and existing under the laws of Germany, having a principal place of business at Binger Str. 173, 55216 Ingelheim, Germany.

6. On information and belief, Alvogen, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 44 Whippany Road, Suite 300, Morristown, New Jersey 07960.

7. On information and belief, Alvogen prepared and submitted Abbreviated New Drug Application No. 211704 ("the ANDA"), and continues to seek FDA approval of the ANDA.

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

JURISDICTION AND VENUE

9. 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 patent-in-suit. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338, and 2201–02.

10. On information and belief, this Court has personal jurisdiction over Alvogen because it is a corporation with a principal place of business in New Jersey.

11. On information and belief, this Court also has jurisdiction over Alvogen because, *inter alia*, this action arises from actions of Alvogen directed toward New Jersey and because Alvogen has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with New Jersey. On information and belief, Alvogen's headquarters is located at 44 Whippany Road, Suite 300, Morristown, New Jersey 07960. Additionally, on information and belief, Alvogen's R&D facility is located at 10 Bloomfield Avenue, Building B, Pine Brook, New Jersey 07058.

12. On information and belief, Alvogen has 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 SPIRIVA® HandiHaler® for sale and use throughout the United States, including this Judicial District. On information and belief, Alvogen has submitted, caused to be submitted, or aided and abetted in the preparation or submission of the ANDA, including activities undertaken from Alvogen's headquarters and/or R&D facility located in New Jersey. On information and belief, in the event that FDA approves the ANDA, Alvogen intends to commercially manufacture, import, market, offer for sale, and sell the ANDA Product throughout the United States and in this Judicial District.

13. At least because, on information and belief, Alvogen has a regular and established place of business in New Jersey and has committed acts of infringement in New Jersey, venue is proper in this Judicial District pursuant to 28 U.S.C. § 1400(b).

BOEHRINGER'S APPROVED SPIRIVA® HANDIHALER® DRUG PRODUCT AND PATENT-IN-SUIT

14. Boehringer makes and sells SPIRIVA® HandiHaler®, a product that is used as an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations. A true and correct copy of the prescribing label for SPIRIVA® HandiHaler® is attached as Exhibit A.

15. Boehringer Ingelheim Pharmaceuticals, Inc. is the holder of New Drug Application (NDA) No. 021395 for SPIRIVA® HandiHaler® and a licensee of the '323 patent. FDA first approved NDA No. 021395 for SPIRIVA® HandiHaler® in January 2004.

16. Boehringer Ingelheim Pharma GmbH & Co. KG owns the '323 patent, which is listed in the Approved Drug Products With Therapeutic Equivalence Evaluations (an FDA publication commonly known as the "Orange Book") for SPIRIVA® HandiHaler®.

17. The '323 patent is entitled "Inhaler and Sieve for an Inhaler" and was duly and lawfully issued by the United States Patent & Trademark Office on April 21, 2015. The '323 patent is attached hereto as Exhibit B.

ALVOGEN'S ANDA

18. On information and belief, Alvogen has submitted or caused to be submitted the 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 inhalation powder, 18 mcg/capsule, as a purported generic version of SPIRIVA® HandiHaler® prior to the expiration of the patent-in-suit.

19. On information and belief, on or about June 9, 2023, Alvogen mailed Boehringer a letter regarding "notice of … information pursuant to 21 U.S.C. § 355(j)(2)(B)(iv), Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act, and 21 C.F.R. § 314.95" ("the Notice Letter"). The Notice Letter represented that Alvogen had submitted to FDA the ANDA and a purported Paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of the product described in the ANDA before the expiration of the patent-in-suit, which is listed in the Orange Book for SPIRIVA® HandiHaler®. Hence, Alvogen's purpose in submitting the ANDA is to manufacture and market the ANDA Product before the expiration of the patent-in-suit.

20. The Notice Letter contained a purported detailed statement of the factual and legal bases for the Paragraph IV certification.

21. On information and belief, Alvogen has participated in the preparation and submission of the ANDA, has provided material support to the preparation and submission of the ANDA, and intends to support the further prosecution of the ANDA.

22. On information and belief, if FDA approves the ANDA, Alvogen 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.

23. Alternatively, on information and belief, if FDA approves the ANDA, Alvogen 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, the ANDA Product is especially adapted for a use that infringes one or more claims of the patent-in-suit and there is no substantial non-infringing use for the ANDA Product.

24. 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 '323 PATENT

25. Boehringer incorporates by reference paragraphs 1–24 as if fully set forth herein.

26. On information and belief, Alvogen has submitted or caused the submission of the ANDA to FDA and continues to seek FDA approval of the ANDA.

27. Alvogen has infringed the '323 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the ANDA with a Paragraph IV certification and seeking FDA approval of the ANDA prior to the expiration of the '323 patent.

28. On information and belief, if the ANDA is approved, Alvogen and its 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 '323 patent.

29. Alvogen's 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 ’323 patent. Accordingly, unless enjoined by this Court, upon FDA approval of the ANDA, Alvogen 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 ’323 patent.

30. Alvogen had actual knowledge of the ’323 patent prior to submitting the ANDA and was aware that the submission of the ANDA with the request for FDA approval prior to the expiration of the ’323 patent would constitute an act of infringement of the ’323 patent. Alvogen 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 ’323 patent.

31. In addition, Alvogen submitted the ANDA without adequate justification for asserting the ’323 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Alvogen’s conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the ’323 patent thus renders this case “exceptional” under 35 U.S.C. § 285.

32. Boehringer will be irreparably harmed if Alvogen is not enjoined from infringing and from actively inducing or contributing to the infringement of the ’323 patent. Boehringer does not have an adequate remedy at law and, considering the balance of hardships between Boehringer and Alvogen, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT II
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE ’323 PATENT

33. Boehringer incorporates by reference paragraphs 1–32 as if fully set forth herein.

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

35. On information and belief, if the 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 Alvogen and its affiliates.

36. On information and belief, Alvogen knows that healthcare professionals or patients will use the ANDA Product in accordance with the labeling sought by the ANDA, and Alvogen will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '323 patent under one or more of 35 U.S.C. §§ 271(a), (b), and (c).

37. On information and belief, Alvogen's 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 the ANDA. Any such conduct before the '323 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '323 patent under one or more of 35 U.S.C. §§ 271(a), (b), and (c).

38. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Boehringer and Alvogen concerning liability for the infringement of the '323 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

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

40. 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 Alvogen has infringed one or more claims of the '323 patent 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), Alvogen's 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 '323 patent;

C. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Alvogen, its affiliates and subsidiaries, and all persons and entities acting in concert with Alvogen, from commercially manufacturing, using, offering for sale, or selling or importing any product that infringes the '323 patent, including the ANDA Product described in ANDA No. 211704;

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. 211704 shall be no earlier than the expiration date of the '323 patent, or any later expiration of exclusivity for the '323 patent, including any extensions or regulatory exclusivities;

E. A declaration under 28 U.S.C. § 2201 that if Alvogen, its officers, agents, servants, employees, licensees, representatives, and attorneys, and any other persons acting or attempting to act in active concert or participation with it or acting on its behalf, engage in the commercial manufacture, use, offer for sale, sale and/or importation of the product described in ANDA No. 211704, it will constitute an act of direct and/or indirect infringement of the '323 patent;

F. An award of damages or other relief, pursuant to 35 U.S.C. § 271(e)(4)(C), if Alvogen engages in the commercial manufacture, use, offer for sale, sale, and/or importation of

the ANDA Product, or any product that infringes the '323 patent, or induces or contributes to such conduct, prior to the expiration of the '323 patent, or any later expiration of exclusivity for the '323 patent, including any extensions or regulatory exclusivities;

G. The entry of a judgment declaring that Alvogen's 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: July 21, 2023

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., Boehringer Ingelheim International GmbH, and Boehringer Ingelheim Pharma GmbH & Co. KG

Of Counsel:

Christopher N. Sipes
R. Jason Fowler
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

I hereby certify that the matter *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Lupin Atlantis Holdings SA, et al.*, Civil Action No. 18-12663 (BRM)(TJB) (D.N.J.) (consolidated) (complaint filed on August 10, 2018; civil case terminated on October 28, 2021) is related to the matter in controversy because the matter in controversy involves the same plaintiffs and because Alvogen is seeking FDA approval to market a generic version of the same pharmaceutical product.

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

Dated: July 21, 2023

Of Counsel:

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

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., Boehringer Ingelheim International GmbH, and Boehringer Ingelheim Pharma GmbH & Co. KG

EXHIBIT A

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

SPIRIVA® HANDIHALER® (tiotropium bromide inhalation powder), for oral inhalation use
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------
SPIRIVA HANDIHALER is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations (1)

----------DOSAGE AND ADMINISTRATION----------
- **For oral inhalation only. DO NOT swallow SPIRIVA capsules. Only use SPIRIVA capsules with the HANDIHALER device** (2)
- Two inhalations of the powder contents of a single SPIRIVA capsule (18 mcg) once daily (2)

----------DOSAGE FORMS AND STRENGTHS----------
Inhalation powder: SPIRIVA capsules contain 18 mcg tiotropium powder for use with HANDIHALER device (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to tiotropium, ipratropium, or any components of SPIRIVA capsules (4)

----------WARNINGS AND PRECAUTIONS----------
- Not for acute use: Not a rescue medication (5.1)
- Immediate hypersensitivity reactions: Discontinue SPIRIVA HANDIHALER at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, urticaria, rash, bronchospasm, or anaphylaxis, occur. Use with caution in patients with severe hypersensitivity to milk proteins. (5.2)
- Paradoxical bronchospasm: Discontinue SPIRIVA HANDIHALER and consider other treatments if paradoxical bronchospasm occurs (5.3)
- 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. (5.4)
- 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. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (>5% incidence in the 1-year placebo-controlled trials) were upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of SPIRIVA HANDIHALER with other anticholinergic-containing drugs. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
Patients with moderate to severe renal impairment should be monitored closely for potential anticholinergic side effects (2, 8.6)

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

Revised: 2/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIRIVA HANDIHALER (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA HANDIHALER is indicated to reduce exacerbations in COPD patients.

2 DOSAGE AND ADMINISTRATION

For oral inhalation only. Do not swallow SPIRIVA capsules, as the intended effects on the lungs will not be obtained. The contents of the SPIRIVA capsules should only be used with the HANDIHALER device *[see Overdosage (10)]***.**

The recommended dose of SPIRIVA HANDIHALER is two inhalations of the powder contents of one SPIRIVA capsule, once-daily, with the HANDIHALER device *[see Patient Counseling Information (17)]*. Do not take more than one dose in 24 hours.

For administration of SPIRIVA HANDIHALER, a SPIRIVA capsule is placed into the center chamber of the HANDIHALER device. The SPIRIVA capsule is pierced by pressing and releasing the green piercing button on the side of the HANDIHALER device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece *[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 SPIRIVA HANDIHALER should be monitored closely for anticholinergic effects *[see Warnings and Precautions (5.6), Use in Specific Populations (8.5, 8.6, 8.7), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder: SPIRIVA HANDIHALER consists of SPIRIVA capsules containing tiotropium powder for oral inhalation and a HANDIHALER device. SPIRIVA capsules contain 18 mcg of tiotropium in a light green, hard gelatin capsule with TI 01 printed on one side and Boehringer Ingelheim company logo on the other side. The HANDIHALER device is only intended for use with the SPIRIVA capsules.

4 CONTRAINDICATIONS

SPIRIVA HANDIHALER is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any components of this product *[see Warnings and Precautions (5.2)]*. In clinical trials and postmarketing experience with SPIRIVA HANDIHALER, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported *[see Warnings and Precautions (5.2)]***.**

5 WARNINGS AND PRECAUTIONS

5.1 Not for Acute Use

SPIRIVA HANDIHALER is intended as a once-daily maintenance treatment for COPD and should not be used for relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

5.2 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 SPIRIVA HANDIHALER. If such a reaction occurs, therapy with SPIRIVA HANDIHALER 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 SPIRIVA HANDIHALER. In addition, SPIRIVA HANDIHALER should be used with caution in patients with severe hypersensitivity to milk proteins.

5.3 Paradoxical Bronchospasm

Inhaled medicines, including SPIRIVA HANDIHALER, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting $beta_2$-agonist such as albuterol. Treatment with SPIRIVA HANDIHALER should be stopped and other treatments considered.

5.4 Worsening of Narrow-Angle Glaucoma

SPIRIVA HANDIHALER 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.

5.5 Worsening of Urinary Retention

SPIRIVA HANDIHALER should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (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.

5.6 Renal Impairment

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA HANDIHALER should be monitored closely for anticholinergic side effects *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

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

- Immediate hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

- Paradoxical bronchospasm *[see Warnings and Precautions (5.3)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.4)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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.

6-Month to 1-Year Trials

The data described below reflect exposure to SPIRIVA HANDIHALER in 2663 patients. SPIRIVA HANDIHALER was studied in two 1-year placebo-controlled trials, two 1-year active-controlled trials, and two 6-month placebo-controlled trials in patients with COPD. In these trials, 1308 patients were treated with SPIRIVA HANDIHALER at the recommended dose of 18 mcg once a day. The population had an age ranging from 39 to 87 years with 65% to 85% males, 95% Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) percent predicted of 39% to 43%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. An additional 6-month trial conducted in a Veteran's Affairs setting is not included in this safety database because only serious adverse events were collected.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, tachycardia, blurred vision, glaucoma (new onset or worsening), dysuria, and urinary retention.

Four multicenter, 1-year, placebo-controlled and active-controlled trials evaluated SPIRIVA HANDIHALER in patients with COPD. Table 1 shows all adverse reactions that occurred with a frequency of ≥3% in the SPIRIVA HANDIHALER group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HANDIHALER group exceeded placebo by ≥1%. The frequency of corresponding reactions in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Reactions (% Patients) in One-Year COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA (n = 550)	Placebo (n = 371)	SPIRIVA (n = 356)	Ipratropium (n = 179)
Body as a Whole				
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (Upper)				
Upper Respiratory Tract Infection	41	37	43	35
Sinusitis	11	9	3	2
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Epistaxis	4	2	1	1
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of ≥3% in the SPIRIVA HANDIHALER treatment group, but were <1% in excess of the placebo group.

Other reactions that occurred in the SPIRIVA HANDIHALER group at a frequency of 1% to 3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole:* allergic reaction, leg pain; *Central and Peripheral Nervous System:* dysphonia, paresthesia; *Gastrointestinal System Disorders:* gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders:* hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders:* skeletal pain; *Cardiac Events:* angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder:* depression; *Infections:* herpes zoster; *Respiratory System Disorder (Upper):* laryngitis; *Vision Disorder:* cataract. In addition, among the adverse reactions observed in the clinical trials with an incidence of <1% were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age *[see Use in Specific Populations (8.5)]*.

Two multicenter, 6-month, controlled studies evaluated SPIRIVA HANDIHALER in patients with COPD. The adverse reactions and the incidence rates were similar to those seen in the 1-year controlled trials.

4-Year Trial

The data described below reflect exposure to SPIRIVA HANDIHALER in 5992 COPD patients in a 4-year placebo-controlled trial. In this trial, 2986 patients were treated with SPIRIVA HANDIHALER at the recommended dose of 18 mcg once a day. The population had an age range from 40 to 88 years, was 75% male, 90% Caucasian, and had COPD with a mean pre-bronchodilator FEV_1 percent predicted of 40%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. When the adverse reactions were analyzed with a frequency of ≥3% in the SPIRIVA HANDIHALER group where the rates in the SPIRIVA HANDIHALER group exceeded placebo by ≥1%, adverse reactions included (SPIRIVA HANDIHALER, placebo): pharyngitis (12.5%, 10.8%), sinusitis (6.5%, 5.3%), headache (5.7%, 4.5%), constipation (5.1%, 3.7%), dry mouth (5.1%, 2.7%), depression (4.4%, 3.3%), insomnia (4.4%, 3.0%), and arthralgia (4.2%, 3.1%).

Additional Adverse Reactions

Other adverse reactions not previously listed that were reported more frequently in COPD patients treated with SPIRIVA HANDIHALER than placebo include: dehydration, skin ulcer, stomatitis, gingivitis, oropharyngeal candidiasis, dry skin, skin infection, and joint swelling.

6.2 Postmarketing Experience

Adverse reactions have been identified during worldwide post-approval use of SPIRIVA HANDIHALER. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

7 DRUG INTERACTIONS

7.1 Sympathomimetics, Methylxanthines, Steroids

SPIRIVA HANDIHALER 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.

7.2 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA HANDIHALER with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.4, 5.5) and Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited human data with SPIRIVA HANDIHALER use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. 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]*.

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.

Data

Animal Data

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).

8.2 Lactation

Risk Summary

There are no data on the presence of tiotropium in human milk, the effects on the breastfed infant, or the effects on milk production. Tiotropium is present in 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 SPIRIVA HANDIHALER and any potential adverse effects on the breastfed child from SPIRIVA HANDIHALER or from the underlying maternal condition.

Data

The distribution of tiotropium bromide into milk was investigated after a single intravenous administration of 10 mg/kg to lactating rats. Tiotropium and/or its metabolites are present in the milk of lactating rats at concentrations above those in plasma.

8.4 Pediatric Use

SPIRIVA HANDIHALER is not indicated for use in children. The safety and effectiveness of SPIRIVA HANDIHALER in pediatric patients have not been established.

8.5 Geriatric Use

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

Of the total number of patients who received SPIRIVA HANDIHALER in the 1-year clinical trials, 426 were <65 years, 375 were 65 to 74 years, and 105 were ≥75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HANDIHALER and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA HANDIHALER group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HANDIHALER group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were –0.6%, 4.6%, and 4.5%. No overall differences in effectiveness were observed among these groups.

8.6 Renal Impairment

Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA HANDIHALER should be monitored closely for anticholinergic side effects *[see Dosage and Administration (2), Warnings and Precautions (5.6), and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

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

10 OVERDOSAGE

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.

Treatment of overdosage consists of discontinuation of SPIRIVA HANDIHALER together with institution of appropriate symptomatic and/or supportive therapy.

Accidental Ingestion

Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from postmarketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HANDIHALER was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

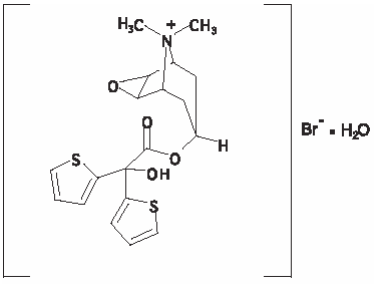
11 DESCRIPTION

SPIRIVA HANDIHALER consists of SPIRIVA capsules and a HANDIHALER device. Each light green, hard gelatin SPIRIVA capsule contains a dry powder consisting of 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate (which may contain milk proteins).

The contents of SPIRIVA capsules are intended for oral inhalation only, and are intended for administration only with the HANDIHALER device.

The active component of SPIRIVA HANDIHALER is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α, 2β, 4β, 5α, 7β)-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 $C_{19}H_{22}NO_4S_2Br \cdot H_2O$.

The HANDIHALER device is an inhalation device used to inhale the dry powder contained in the SPIRIVA capsule. The dry powder is delivered from the HANDIHALER device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HANDIHALER device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2 L total). In a study of 26 adult patients with COPD and severely compromised lung function [mean FEV_1 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16% to 65%)], the median peak inspiratory flow (PIF) through the HANDIHALER device was 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HANDIHALER device, which may vary from patient to patient, and may vary with the exposure time of the SPIRIVA capsule outside the blister pack.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, 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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

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 to 60 msec was higher in the SPIRIVA HANDIHALER 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 studies with SPIRIVA HANDIHALER did not detect an effect of the drug on QTc intervals.

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 dry powder for inhalation 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 dry powder for inhalation 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

12.3 Pharmacokinetics

Tiotropium is administered by dry powder inhalation. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy. A dedicated pharmacokinetic study in patients with COPD evaluating once-daily tiotropium delivered from the RESPIMAT inhaler (5 mcg) and as inhalation powder (18 mcg) from the HANDIHALER device resulted in a similar systemic exposure between the two products.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of tiotropium. Maximum tiotropium plasma concentrations were observed 7 minutes after inhalation.

Distribution

Tiotropium is 72% bound to plasma protein and had a volume of distribution of 32 L/kg after intravenous administration to young healthy volunteers. 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 readily penetrate the blood-brain barrier.

Elimination

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 intravenous administration in young healthy volunteers. After chronic once-daily dry powder inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Metabolism

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, neither of which binds 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 II 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 did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Excretion

Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). After dry powder inhalation to COPD patients at steady state, urinary excretion was 7% (1.3mcg) of the unchanged dose over 24 hours. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.

Specific Populations

Geriatric Patients

As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (365 mL/min in COPD patients <65 years to 271 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 following administration via HANDIHALER device.

Renal Impairment

Following 4-week SPIRIVA HANDIHALER or SPIRIVA RESPIMAT once daily dosing in patients with COPD, mild renal impairment (creatinine clearance 60-<90 mL/min) resulted in 6-23% higher $AUC_{0-6,ss}$ and 6-17% higher $C_{max,ss}$ values; moderate renal impairment (creatinine clearance 30-<60 mL/min) resulted in 54-57%

higher $AUC_{0-6,ss}$ and 15-31% higher $C_{max,ss}$ values compared to COPD patients with normal renal function (creatinine clearance ≥90 mL/min). There is insufficient data for tiotropium exposure in patients with severe renal impairment (creatinine clearance <30 mL/min) following inhalation of SPIRIVA HANDIHALER or SPIRIVA RESPIMAT. However AUC_{0-4} and C_{max} were 94% and 52% higher, respectively, in patients with severe renal impairment following intravenous infusion of tiotropium bromide.

Hepatic Impairment

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

Drug Interactions

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 (MRHDID) 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 assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

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 40 times the MRHDID on a mcg/m^2 basis). No such effects were observed at 9 mcg/kg/day (approximately 5 times the MRHDID on a mcg/m^2 basis). The fertility index, however, was not affected at inhalation doses up to 1689 mcg/kg/day (approximately 910 times the MRHDID on a mcg/m^2 basis).

14 CLINICAL STUDIES

The SPIRIVA HANDIHALER (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2663 patients with COPD (1308 receiving SPIRIVA HANDIHALER): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a forced expiratory volume in one second (FEV_1) less than or equal to 60% or 65% of predicted, and a ratio of FEV_1/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HANDIHALER, administered once-daily in the morning, provided improvement in lung function (FEV_1), with peak effect occurring within 3 hours following the first dose.

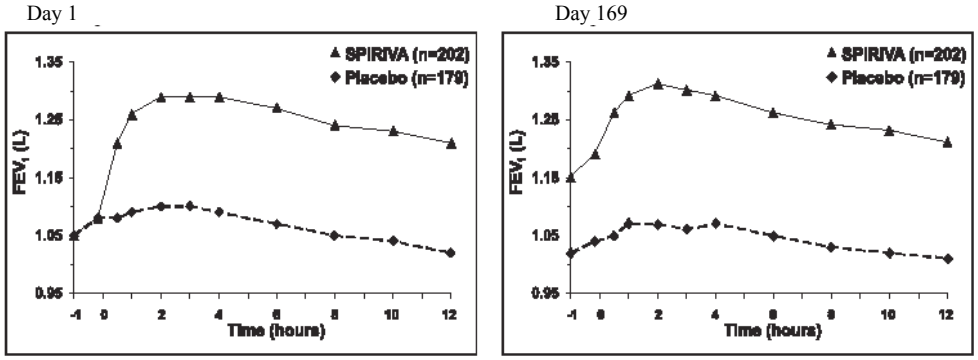
Two additional trials evaluated exacerbations: a 6-month, randomized, double-blind, placebo-controlled, multicenter clinical trial of 1829 COPD patients in a US Veterans Affairs setting and a 4-year, randomized, double-blind, placebo-controlled, multicenter, clinical trial of 5992 COPD patients. Long-term effects on lung function and other outcomes, were also evaluated in the 4-year multicenter trial.

6-Month to 1-Year Effects on Lung Function

In the 1-year, placebo-controlled trials, the mean improvement in FEV_1 at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (Day 1). Further improvements in FEV_1 and forced vital capacity (FVC) were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV_1, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV_1 values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV_1) with SPIRIVA HANDIHALER, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

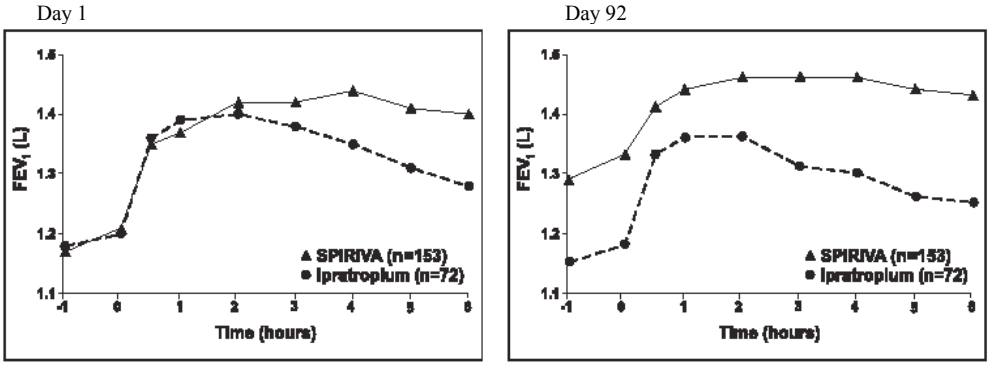
Figure 1 Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HANDIHALER and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

Results of each of the 1-year ipratropium-controlled trials were similar to the results of the 1-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV_1 Over Time (0 to 6 hours post-dose) on Days 1 and 92, Respectively for One of the Two Ipratropium-Controlled Studies*



*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HANDIHALER and ipratropium groups, respectively, completed through 3 months of observation. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HANDIHALER was administered in the morning or in the evening.

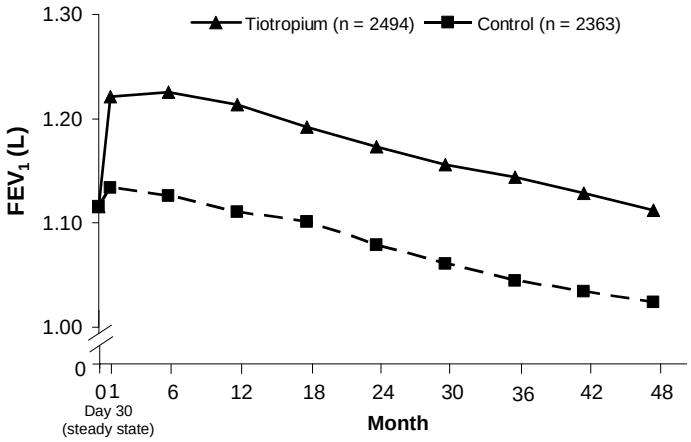
Throughout each week of the 1-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HANDIHALER had a reduced requirement for the use of rescue short-acting $beta_2$-agonists. Reduction in the use of rescue short-acting $beta_2$-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

4-Year Effects on Lung Function

A 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial involving 5992 COPD patients was conducted to evaluate the long-term effects of SPIRIVA HANDIHALER on disease progression (rate of decline in FEV_1). Patients were permitted to use all respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. The patients were 40 to 88 years of age, 75% male, and 90% Caucasian with a diagnosis of COPD and a mean pre-bronchodilator FEV_1 of 39% predicted (range = 9% to 76%) at study entry. There was no difference between the groups in either of the co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV_1, as demonstrated by similar slopes of FEV_1 decline over time (Figure 3).

SPIRIVA HANDIHALER maintained improvements in trough (pre-dose) FEV_1 (adjusted means over time: 87 to 103 mL) throughout the 4 years of the study (Figure 3).

Figure 3 Trough (pre-dose) FEV_1 Mean Values at Each Time Point



Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV_1 (observed mean) = 1.12. Patients with ≥3 acceptable pulmonary function tests after Day 30 and non-missing baseline value were included in the analysis.

Exacerbations

The effect of SPIRIVA HANDIHALER on COPD exacerbations was evaluated in two clinical trials: a 4-year clinical trial described above and a 6-month clinical trial of 1829 COPD patients in a Veterans Affairs setting. In the 6-month trial, COPD exacerbations were defined as a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics, systemic steroids, or hospitalization. The population had an age ranging from 40 to 90 years with 99% males, 91% Caucasian, and had COPD with a mean pre-bronchodilator FEV_1 percent predicted of 36% (range = 8% to 93%). Patients were permitted to use respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. In the 6-month trial, the co-primary endpoints were the proportion of patients with COPD exacerbation and the proportion of patients with hospitalization due to COPD exacerbation. SPIRIVA HANDIHALER significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo (27.9% vs. 32.3%, respectively; Odds Ratio (OR) (tiotropium/placebo) = 0.81; 95% CI = 0.66, 0.99; p = 0.037). The proportion of patients with hospitalization due to COPD exacerbations in patients who used SPIRIVA HANDIHALER compared to placebo was 7.0% vs. 9.5%, respectively; OR = 0.72; 95% CI = 0.51, 1.01; p = 0.056.

Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids. SPIRIVA HANDIHALER significantly reduced the risk of an exacerbation by 14% (Hazard Ratio (HR) = 0.86; 95% CI = 0.81, 0.91; p<0.001) and reduced the risk of exacerbation-related hospitalization by 14% (HR = 0.86; 95% CI = 0.78, 0.95; p<0.002) compared to placebo. The median time to first exacerbation was delayed from 12.5 months (95% CI = 11.5, 13.8) in the placebo group to 16.7 months (95% CI = 14.9, 17.9) in the SPIRIVA HANDIHALER group.

All-Cause Mortality

In the 4-year placebo-controlled lung-function trial described above, all-cause mortality compared to placebo was assessed. There were no significant differences in all-cause mortality rates between SPIRIVA HANDIHALER and placebo.

The all-cause mortality of SPIRIVA HANDIHALER was also compared to tiotropium inhalation spray 5 mcg (SPIRIVA RESPIMAT 5 mcg) in an additional long-term, randomized, double-blind, double-dummy active-controlled study with an observation period up to 3 years. All-cause mortality was similar between SPIRIVA HANDIHALER and SPIRIVA RESPIMAT.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPIRIVA HANDIHALER consists of SPIRIVA capsules and the HANDIHALER device. SPIRIVA capsules contain 18 mcg of tiotropium and are light green, with the Boehringer Ingelheim company logo on the SPIRIVA capsule cap and TI 01 on the SPIRIVA capsule body, or vice versa.

The HANDIHALER device is gray colored with a green piercing button. It is imprinted with SPIRIVA HANDIHALER (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo. It is also imprinted to indicate that SPIRIVA capsules should not be stored in the HANDIHALER device and that the HANDIHALER device is only to be used with SPIRIVA capsules.

SPIRIVA capsules are packaged in an aluminum/aluminum blister card and joined along a perforated-cut line. SPIRIVA capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual SPIRIVA capsule is opened.

The following packages are available:

- carton containing 5 SPIRIVA capsules (1 unit-dose blister card) and 1 HANDIHALER inhalation device (NDC 0597-0075-75) (institutional pack)
- carton containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HANDIHALER inhalation device (NDC 0597-0075-41)
- carton containing 90 SPIRIVA capsules (9 unit-dose blister cards) and 1 HANDIHALER inhalation device (NDC 0597-0075-47)

Keep out of reach of children. Do not get powder into eyes.

Storage
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

The SPIRIVA capsules should not be exposed to extreme temperature or moisture. Do not store SPIRIVA capsules in the HANDIHALER device.

17 PATIENT COUNSELING INFORMATION

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

Not for Acute Use:

Instruct patients that SPIRIVA HANDIHALER is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems (i.e., as a rescue medication).

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 SPIRIVA HANDIHALER. Advise patient to immediately discontinue treatment and consult a physician should any of these signs or symptoms develop.

Paradoxical Bronchospasm:

Inform patients that SPIRIVA HANDIHALER can produce paradoxical bronchospasm. Advise patients that if paradoxical bronchospasm occurs, patients should discontinue SPIRIVA HANDIHALER.

Worsening of Narrow-Angle Glaucoma:

Instruct patients to be alert for signs and symptoms of 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 and symptoms develop.

Inform patients that care must be taken not to allow the powder 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 SPIRIVA HANDIHALER, caution patients about engaging in activities such as driving a vehicle or operating appliances or machinery.

Worsening of Urinary Retention:

Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Instructions for Administering SPIRIVA HANDIHALER:

Instruct patients on how to correctly administer SPIRIVA capsules using the HANDIHALER device *[see Patient Counseling Information (17)]*. Instruct patients that SPIRIVA capsules should only be administered via the HANDIHALER device and the HANDIHALER device should not be used for administering other medications. **Remind patients that the contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed**.

Instruct patients always to store SPIRIVA capsules in sealed blisters and to remove only one SPIRIVA capsule immediately before use or its effectiveness may be reduced. Instruct patients to discard unused additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use).

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

Address medical inquiries to: (800) 542-6257 or (800) 459-9906 TTY.

IT5300LA262018

Patient Information

SPIRIVA® (speh REE vah) HANDIHALER®
(tiotropium bromide inhalation powder)

	**Do NOT swallow SPIRIVA capsules.**

Important Information: Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HANDIHALER device and inhaled through your mouth (oral inhalation).

Read the information that comes with your SPIRIVA HANDIHALER before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is SPIRIVA HANDIHALER?

- SPIRIVA HANDIHALER is a prescription medicine used each day (a maintenance medicine) to control symptoms of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
- SPIRIVA HANDIHALER helps make your lungs work better for 24 hours. SPIRIVA HANDIHALER relaxes your airways and helps keep them open. You may start to feel like it is easier to breathe on the first day, but it may take longer for you to feel the full effects of the medicine. SPIRIVA HANDIHALER works best and may help make it easier to breathe when you use it every day.
- SPIRIVA HANDIHALER reduces the likelihood of flare-ups and worsening of COPD symptoms (COPD exacerbations). A COPD exacerbation is defined as an increase or new onset of more than one COPD symptom such as cough, mucus, shortness of breath, and wheezing that requires medicine beyond your rescue medicine.

SPIRIVA HANDIHALER is not a rescue medicine and should not be used for treating sudden breathing problems. Your doctor may give you other medicine to use for sudden breathing problems.

It is not known if SPIRIVA HANDIHALER is safe and effective in children.

Who should not take SPIRIVA HANDIHALER?

Do not use SPIRIVA HANDIHALER if you:

- are allergic to tiotropium, ipratropium (Atrovent®), or any of the ingredients in SPIRIVA HANDIHALER. See the end of this leaflet for a complete list of ingredients in SPIRIVA HANDIHALER.

Symptoms of a serious allergic reaction to SPIRIVA HANDIHALER may include:

- raised red patches on your skin (hives)
- itching
- rash
- swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

If you have these symptoms of an allergic reaction, stop taking SPIRIVA HANDIHALER and call your doctor right away or go to the nearest hospital emergency room.

What should I tell my doctor before using SPIRIVA HANDIHALER?

Before taking SPIRIVA HANDIHALER, tell your doctor about all your medical conditions, including if you:

- have kidney problems.
- have glaucoma. SPIRIVA HANDIHALER may make your glaucoma worse.
- have an enlarged prostate, problems passing urine, or a blockage in your bladder. SPIRIVA HANDIHALER may make these problems worse.
- are pregnant or plan to become pregnant. It is not known if SPIRIVA HANDIHALER could harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if SPIRIVA HANDIHALER passes into breast milk. You and your doctor will decide if SPIRIVA HANDIHALER is right for you while you breast-feed.
- have a severe allergy to milk proteins. Ask your doctor if you are not sure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and eye drops, vitamins, and herbal supplements. Some of your other medicines or supplements may affect the way SPIRIVA HANDIHALER works. SPIRIVA HANDIHALER is an anticholinergic medicine. You should not take other anticholinergic medicines while using SPIRIVA HANDIHALER, including ipratropium. Ask your doctor or pharmacist if you are not sure if one of your medicines is an anticholinergic.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I take SPIRIVA HANDIHALER?

- Use SPIRIVA HANDIHALER exactly as prescribed. Use SPIRIVA HANDIHALER one time every day.
- Read the "Instructions for Use" at the end of this leaflet before you use SPIRIVA HANDIHALER. Talk with your doctor if you do not understand the instructions.
- **Do not swallow SPIRIVA capsules.**
- **Only use SPIRIVA capsules with the HANDIHALER device.**
- **Do not use the HANDIHALER device to take any other medicine**.
- SPIRIVA HANDIHALER comes as a powder in a SPIRIVA capsule that fits the HANDIHALER device. Each SPIRIVA capsule, containing only a small amount of SPIRIVA powder, is one full dose of medicine.
- Separate one blister from the blister card. Then take out one of the SPIRIVA capsules from the blister package right before you use it.
- After the capsule is pierced, take a complete dose of SPIRIVA HANDIHALER by breathing in the powder by mouth two times, using the HANDIHALER device (take 2 inhalations from one SPIRIVA capsule). See the "**Instructions for Use**" at the end of this leaflet.
- Throw away any SPIRIVA capsule that is not used right away after it is taken out of the blister package. Do not leave the SPIRIVA capsules open to air; they may not work as well.
- If you miss a dose, take it as soon as you remember. Do not use SPIRIVA HANDIHALER more than one time every 24 hours.
- If you use more than your prescribed dose of SPIRIVA HANDIHALER, call your doctor or a poison control center.

What should I avoid while using SPIRIVA HANDIHALER?

- Do not let the powder from the SPIRIVA capsule get into your eyes. Your vision may get blurry and the pupil in your eye may get larger (dilate). If this happens, call your doctor.
- SPIRIVA HANDIHALER can cause dizziness and blurred vision. Should you experience these symptoms you should use caution when engaging in activities such as driving a car or operating appliances or other machines.

What are the possible side effects of SPIRIVA HANDIHALER?

SPIRIVA HANDIHALER can cause serious side effects, including: Allergic reaction. Symptoms may include**:**

- raised red patches on your skin (hives)
- itching
- rash
- swelling of the lips, tongue, or throat that may cause difficulty in breathing or swallowing

If you have these symptoms of an allergic reaction, stop taking SPIRIVA HANDIHALER and call your doctor right away or

go to the nearest hospital emergency room.

- **Sudden narrowing and blockage of the airways into the lungs (bronchospasm).** Your breathing suddenly gets worse.

If you have these symptoms of bronchospasm, stop taking SPIRIVA HANDIHALER and call your doctor right away or go to the nearest hospital emergency room.

- **New or worsened increased pressure in the eyes (acute narrow-angle glaucoma).** Symptoms of acute narrow-angle glaucoma may include:
    - eye pain
    - blurred vision
    - seeing halos (visual halos) or colored images along with red eyes

Using only eye drops to treat these symptoms may not work. If you have these symptoms, stop taking SPIRIVA HANDIHALER and call your doctor right away.

- **New or worsened urinary retention.** Symptoms of blockage in your bladder and/or enlarged prostate may include: difficulty passing urine, painful urination.

If you have these symptoms of urinary retention, stop taking SPIRIVA HANDIHALER and call your doctor right away.

Other side effects with SPIRIVA HANDIHALER include:

- upper respiratory tract infection
- dry mouth
- sinus infection
- sore throat
- non-specific chest pain
- urinary tract infection
- indigestion
- runny nose
- constipation
- increased heart rate
- blurred vision

These are not all the possible side effects with SPIRIVA HANDIHALER. Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SPIRIVA HANDIHALER?

- **Do not store SPIRIVA capsules in the HANDIHALER device.**
- Store SPIRIVA capsules in the sealed blister package at room temperature 68°F to 77°F (20°C to 25°C).
- Keep SPIRIVA capsules away from heat and cold (do not freeze).
- Store SPIRIVA capsules in a dry place. Throw away any unused SPIRIVA capsules that have been open to air.

Ask your doctor or pharmacist if you have any questions about storing your SPIRIVA capsules.

Keep SPIRIVA HANDIHALER, SPIRIVA capsules, and all medicines out of the reach of children.

General information about SPIRIVA HANDIHALER

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use SPIRIVA HANDIHALER for a purpose for which it has not been prescribed. Do not give SPIRIVA HANDIHALER to other people even if they have the same symptoms that you have. It may harm them.

For more information about SPIRIVA HANDIHALER, talk with your doctor. You can ask your doctor or pharmacist for information about SPIRIVA HANDIHALER that is written for health professionals.

For more information about SPIRIVA HANDIHALER, go to www.SPIRIVA.com, or scan the code below, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in SPIRIVA HANDIHALER?

Active ingredient: tiotropium
Inactive ingredient: lactose monohydrate

What is COPD (Chronic Obstructive Pulmonary Disease)?

COPD is a serious lung disease that includes chronic bronchitis, emphysema, or both. Most COPD is caused by smoking. When you have COPD, your airways become narrow. So, air moves out of your lungs more slowly. This makes it hard to breathe.

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

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

Licensed from:
Boehringer Ingelheim International GmbH

SPIRIVA® and HANDIHALER® are registered trademarks and are used under license from Boehringer Ingelheim International GmbH.

Revised: February 2018

IT5300LA262018

Instructions for Use

SPIRIVA® (speh REE vah) **HANDIHALER®**
(tiotropium bromide inhalation powder)

Do not swallow SPIRIVA capsules.

Important Information about using your SPIRIVA HANDIHALER

- **Do not swallow SPIRIVA capsules.**
- **SPIRIVA capsules should only be used with the HANDIHALER device and inhaled through your mouth (oral inhalation).**
- **Do not use your HANDIHALER device to take any other medicine.**

First read the Patient Information, then read these Instructions for Use before you start to use SPIRIVA HANDIHALER and each time you refill your prescription. There may be new information.

Becoming familiar with your HANDIHALER device and SPIRIVA capsules:

Your SPIRIVA HANDIHALER comes with SPIRIVA capsules in blister packaging and a HANDIHALER device. Use the new HANDIHALER device provided with your medicine.

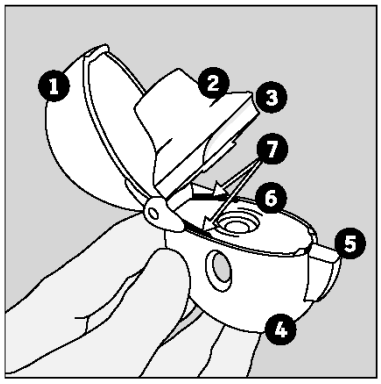


Figure A

The parts of your HANDIHALER device include:
(See Figure A)

1. dust cap (lid)
2. mouthpiece
3. mouthpiece ridge
4. base
5. green piercing button
6. center chamber
7. air intake vents

Figure B

Each SPIRIVA capsule is packaged in a blister. (See Figure B)

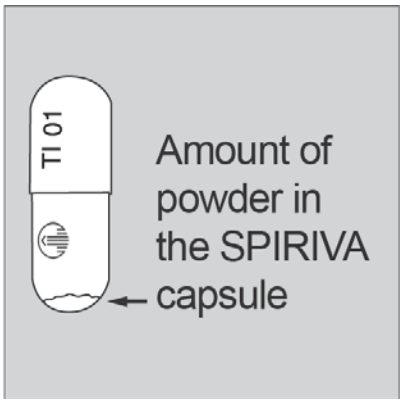


Figure C

- Each SPIRIVA capsule contains only a small amount of powder. (See Figure C) This is 1 full dose.
- **Do not open the SPIRIVA capsule** or it may not work.

Taking your full daily dose of medicine requires 4 main steps.

Step 1. Opening your HANDIHALER device:

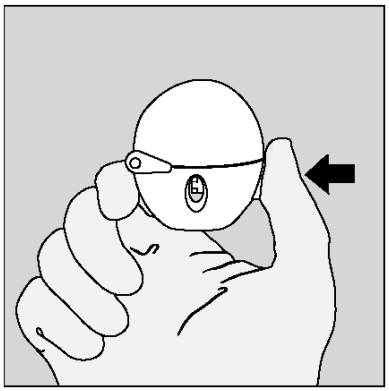


Figure D

After removing your HANDIHALER device from the pouch:

- Open the dust cap (lid) by pressing the green piercing button. (See Figure D)

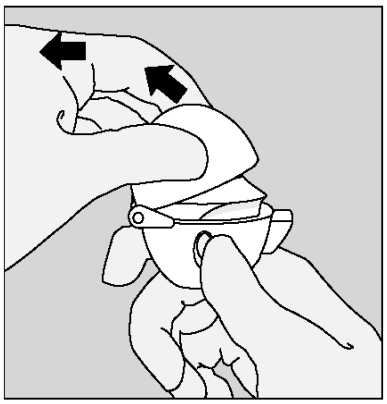


Figure E

- Pull the dust cap (lid) upwards away from the base to expose the mouthpiece. (See Figure E)

Figure F

- Open the mouthpiece by pulling the mouthpiece ridge up and away from the base so the center chamber is showing. (See Figure F)

Step 2. Inserting the SPIRIVA capsule into your HANDIHALER device:

Figure G

Each day, separate only 1 of the blisters from the blister card by tearing along the perforated line. (See Figure G)

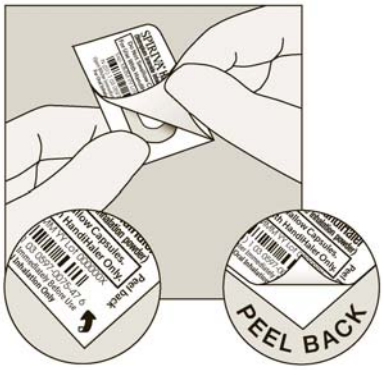


Figure H

Remove the SPIRIVA capsule from the blister:

- **Do not** cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.
- Bend 1 of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole SPIRIVA capsule. (See Figure H)
- If you have opened more than 1 blister to the air, the extra SPIRIVA capsule should not be used and should be thrown away.

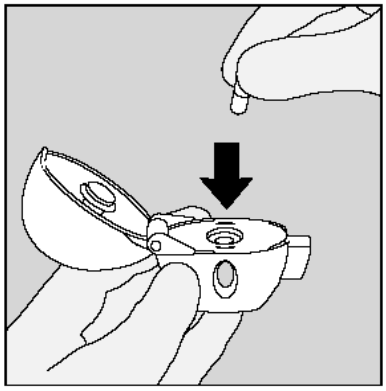


Figure I

Place the SPIRIVA capsule in the center chamber of your HANDIHALER device. (See Figure I)

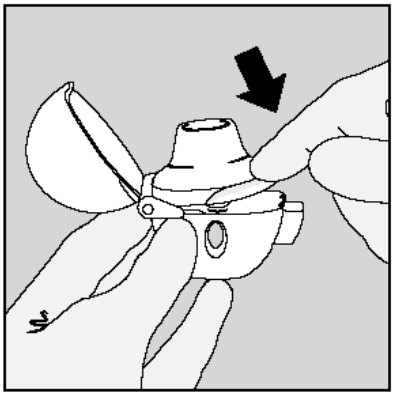


Figure J

Close the mouthpiece firmly against the gray base until you hear a click. Leave the dust cap (lid) open. (See Figure J)

Step 3. Piercing the SPIRIVA capsule:

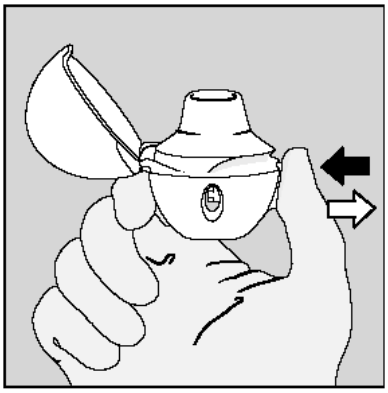


Figure K

- Hold your HANDIHALER device with the mouthpiece pointed up. (See Figure K)
- Press the green piercing button once until it is flat (flush) against the base, then release. This is how you make holes in the SPIRIVA capsule so that you get your medicine when you breathe in.
- **Do not** press the green button more than one time.
- **Do not** shake your HANDIHALER device.
- The piercing of the SPIRIVA capsule may produce small gelatin pieces. Some of these small pieces may pass through the screen of your HANDIHALER device into your mouth or throat when you breathe in your medicine. This is normal. The small pieces of gelatin should not harm you.

Step 4. Taking your full daily dose (2 inhalations from the same SPIRIVA capsule):

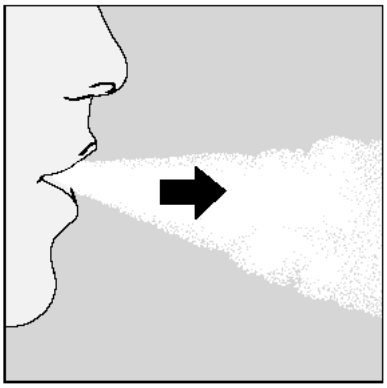


Figure L

Breathe out completely in 1 breath, emptying your lungs of any air. (See Figure L)

Important: Do not breathe into your HANDIHALER device.

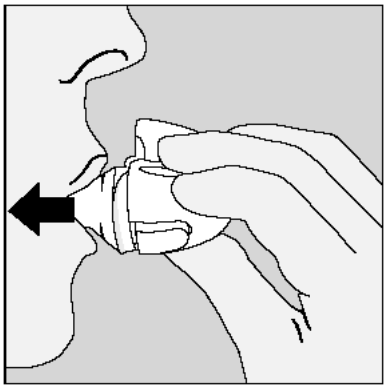


Figure M

With your next breath, take your medicine:

- **Hold your head in an upright position while you are looking straight ahead.** (See Figure M)
- Raise your HANDIHALER device to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the SPIRIVA capsule vibrate** (rattle). (See Figure M)
- Hold your breath for a few seconds and, at the same time, take your HANDIHALER device out of your mouth.
- Breathe normally again.

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, “If you do not hear or feel the SPIRIVA capsule rattle as you breathe in your medicine.”

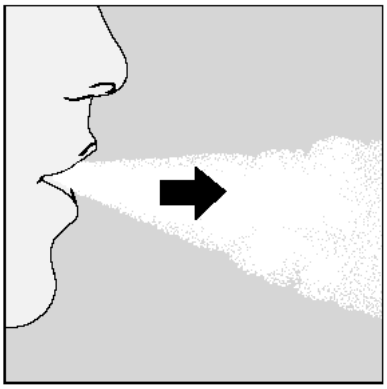


Figure N

To get your full daily dose, you must again, breathe out completely (See Figure N) and for a second time, breathe in (See Figure O) from the same SPIRIVA capsule.

Important: Do not press the green piercing button again.

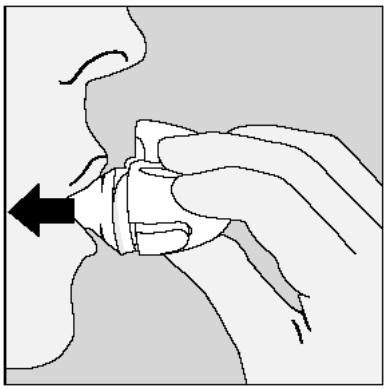


Figure O

Remember: To get your full medicine dose each day, you must breathe in 2 times from the same SPIRIVA capsule. Make sure you breathe out completely each time before you breathe in from your HANDIHALER device.

Caring for and storing your SPIRIVA HANDIHALER:

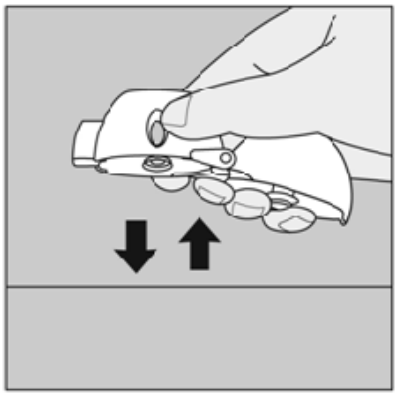


Figure P

- After taking your daily dose, open the mouthpiece and tip out the used SPIRIVA capsule into your trash can, without touching it.
- Remove any SPIRIVA capsule pieces or SPIRIVA powder buildup by turning your HANDIHALER device upside down and gently, but firmly, tapping it. (See Figure P) Then, close the mouthpiece and dustcap for storage.
- **Do not** store your HANDIHALER device and SPIRIVA capsules (blisters) in a damp moist place. Always store SPIRIVA capsules in the sealed blisters.

If you do not hear or feel the SPIRIVA capsule rattle as you breathe in your medicine:

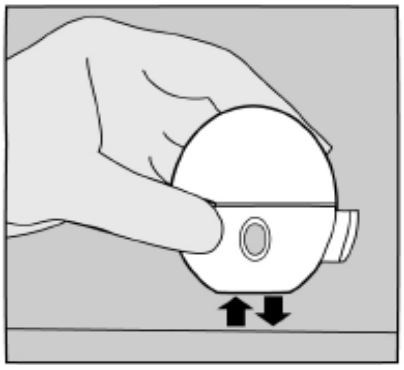


Figure Q

Do not press the green piercing button again.

Hold your HANDIHALER device with the mouthpiece pointed up and tap your HANDIHALER device gently on a table. (See Figure Q)

Check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth. (See Figure O)

If you still do not hear or feel the SPIRIVA capsule rattle after repeating the above steps:

- Throw away the SPIRIVA capsule.
- Open the base by lifting the green piercing button and check the center chamber for pieces of the SPIRIVA capsule. SPIRIVA capsule pieces in the center chamber can cause a SPIRIVA capsule not to rattle.
- Turn your HANDIHALER device upside down and gently, but firmly, tap to remove the SPIRIVA capsule pieces. Call your doctor for instructions.

Cleaning your HANDIHALER device:

Figure R

Clean your HANDIHALER device as needed. (See Figure R)

- **It takes 24 hours to air dry your HANDIHALER device** after you clean it.
- **Do not** use cleaning agents or detergents.
- **Do not** place your HANDIHALER device in the dishwasher for cleaning.

Cleaning Steps:

- Open the dust cap and mouthpiece.
- Open the base by lifting the green piercing button.
- Look in the center chamber for SPIRIVA capsule pieces or powder buildup. If seen, tap out.
- Rinse your HANDIHALER device with warm water, pressing the green piercing button a few times so that the center chamber and the piercing needle is under the running water. Check that any powder buildup or SPIRIVA capsule pieces are removed.
- Dry your HANDIHALER device well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open by fully spreading it out so that it dries completely.
- **Do not** use a hair dryer to dry your HANDIHALER device.
- **Do not** use your HANDIHALER device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

Helpful Hints to help ensure that you are properly taking your full daily dose of SPIRIVA HANDIHALER:

- **Press** the green piercing button **1 time; Breathe in 2 times; Breathe out completely** before each of the **2** inhalations.
- Always use the new HANDIHALER device provided with your medicine.
- Keep your HANDIHALER device with the mouthpiece pointed up when pressing the green piercing button.
- **Press the green piercing button 1 time** to pierce the SPIRIVA capsule.
- Do not breathe out into your HANDIHALER device.
- Keep your HANDIHALER device in a horizontal position and keep your head upright, looking straight ahead, when breathing in.
- Check the center chamber of your HANDIHALER device for SPIRIVA capsule pieces or powder build-up. If pieces or powder are seen, tap out before use.
- Clean your HANDIHALER as needed and dry thoroughly.

For more information, ask your doctor or pharmacist, or go to www.spiriva.com, or scan the code below, or call 1-800-542-6257 or (TTY) 1-800-459-9906.

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

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

Licensed from:
Boehringer Ingelheim International GmbH

Revised: February 2018

IT5300LA262018

EXHIBIT B

US009010323B2

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

(10) **Patent No.: US 9,010,323 B2**
(45) **Date of Patent: Apr. 21, 2015**

(54) **INHALER AND SIEVE FOR AN INHALER**

(75) Inventors: **Lukas Haerder**, Bad Neustadt/Saale (DE); **Claus Breuer**, Ennigerloh (DE)

(73) Assignee: **Boehringer Ingelheim Pharma GmbH & Co. KG**, 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 404 days.

(21) Appl. No.: **12/921,447**

(22) PCT Filed: **Mar. 11, 2009**

(86) PCT No.: **PCT/EP2009/052858**
§ 371 (c)(1),
(2), (4) Date: **Oct. 11, 2010**

(87) PCT Pub. No.: **WO2009/112521**
PCT Pub. Date: **Sep. 17, 2009**

(65) **Prior Publication Data**

US 2011/0120465 A1 May 26, 2011

(30) **Foreign Application Priority Data**

Mar. 13, 2008 (DE) 10 2008 014 025

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

(52) **U.S. Cl.**
CPC ***A61M 15/0028*** (2013.01); *A61M 2202/064* (2013.01); ***A61M 11/003*** (2013.01); ***A61M 15/0026*** (2013.01); ***A61M 15/003*** (2013.01); ***A61M 15/0035*** (2013.01)

(58) **Field of Classification Search**
CPC B01D 39/12; B01D 71/024; B01D 9/12; B01D 7/02; B01D 39/1623; B60R 21/2644; A61M 2202/064; A61M 15/0028; A61M 16/0808; A62B 7/02; A62B 9/04; A62B 7/10; A62B 23/025; A41D 13/11
USPC 128/200.18, 203.19, 203.21; 96/362, 96/363; 222/189.09
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,380,182 A * 7/1945 La Bille 128/203.23
2,456,621 A * 12/1948 Cheney, Jr. 264/127
(Continued)

FOREIGN PATENT DOCUMENTS

CA 2507579 A1 6/2004
DE 8801555 U1 6/1988
(Continued)

OTHER PUBLICATIONS

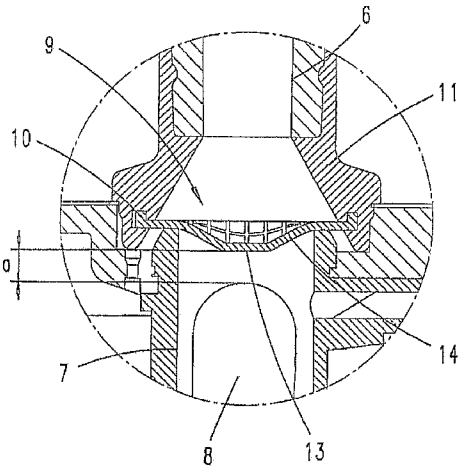
International Search Report for PCT/EP2009/052828 mailed Jun. 6, 2009.
(Continued)

Primary Examiner — Tan-Uyen (Jackie) T Ho
Assistant Examiner — Mark Wardas
(74) *Attorney, Agent, or Firm* — Michael P. Morris; Wendy A. Petka

(57) **ABSTRACT**

An inhaler (**1**) includes a sieve part (**9**) for administrating powdered substances such as medical substances. The inhaler (**1**) includes a suction air channel (**6**) leading to a mouthpiece (**4**), a substance supply container (**8**) that is moveable inside a receiving chamber (**7**) and the sieve part (**9**) disposed in the suction air channel (**6**) between the receiving chamber (**7**) and the mouthpiece (**4**). The sieve part includes a retaining edge (**10**), a sieve area contained in a cross sectional area within the retaining edge (**10**), and a protruding area (**12**) that protrudes to one side and has a flat portion (**13**).

22 Claims, 4 Drawing Sheets



(51) **Int. Cl.**

A61M 16/00	(2006.01)
B05D 7/14	(2006.01)
B65D 83/06	(2006.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,741,319	A *	4/1956	Mickelsen	169/87
3,483,980	A	12/1969	Cochran	
3,499,677	A *	3/1970	Callon et al.	296/170
4,846,168	A *	7/1989	Abiko et al.	128/203.15
4,918,017	A	4/1990	Greenstreet et al.	
4,995,385	A *	2/1991	Valentini et al.	128/203.21
5,401,406	A *	3/1995	Johnson et al.	210/323.2
5,460,173	A *	10/1995	Mulhauser et al.	128/203.15
5,582,205	A *	12/1996	McCarty et al.	137/545
5,647,347	A *	7/1997	Van Oort	128/203.15
6,250,301	B1 *	6/2001	Pate	128/203.26
7,025,059	B2 *	4/2006	Pera	128/203.21
7,669,617	B2 *	3/2010	Parks et al.	141/241
2002/0158150	A1	10/2002	Matsugi et al.	
2004/0149283	A1 *	8/2004	Hochrainer	128/203.15
2009/0277446	A1 *	11/2009	Walz	128/203.15
2010/0269819	A1 *	10/2010	Sievers et al.	128/200.23

FOREIGN PATENT DOCUMENTS

DE	102006016904	A1 *	10/2007
GB	2253200	A	9/1992
WO	9747347	A1	12/1997
WO	2004047796	A2	6/2004
WO	2007118801	A1	10/2007

OTHER PUBLICATIONS

Abstract in English for DE8801555, downloaded from espacenet Sep. 7, 2010.

* cited by examiner

Fig. 1

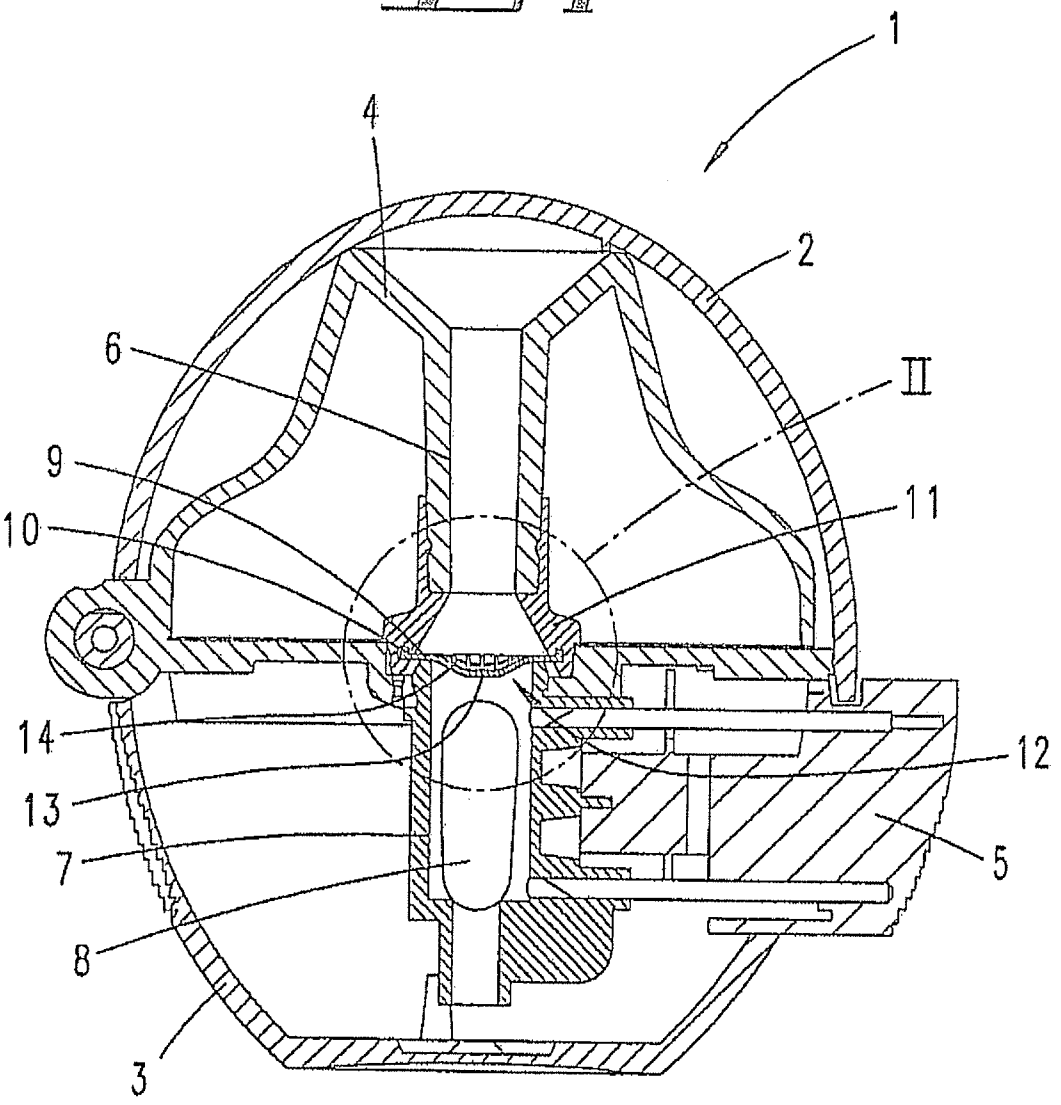


Fig. 2

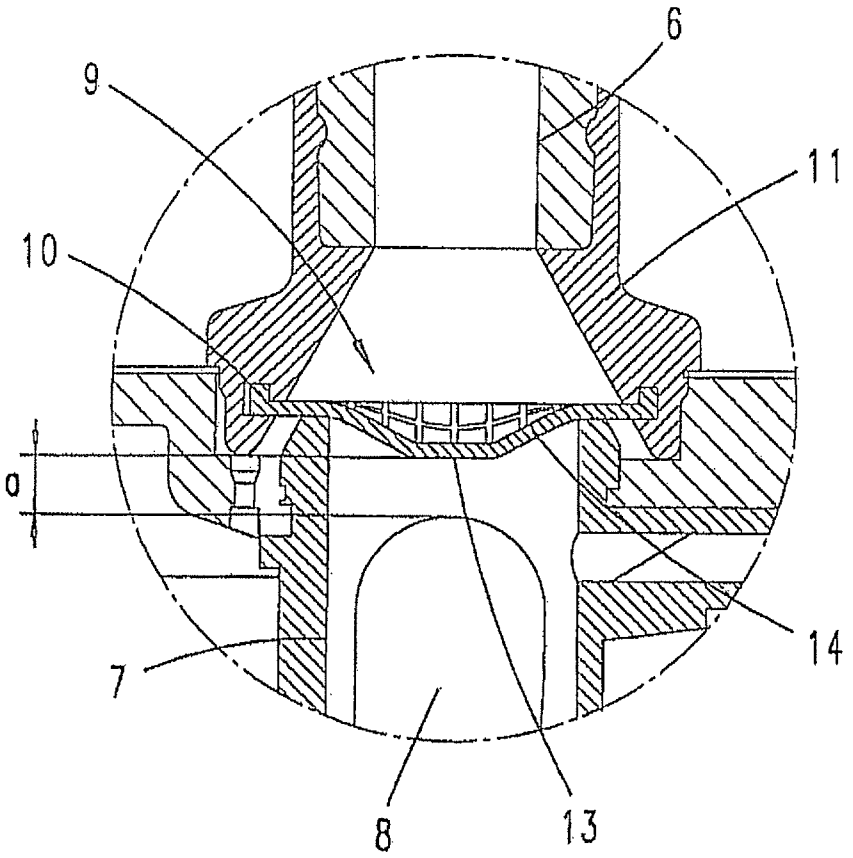
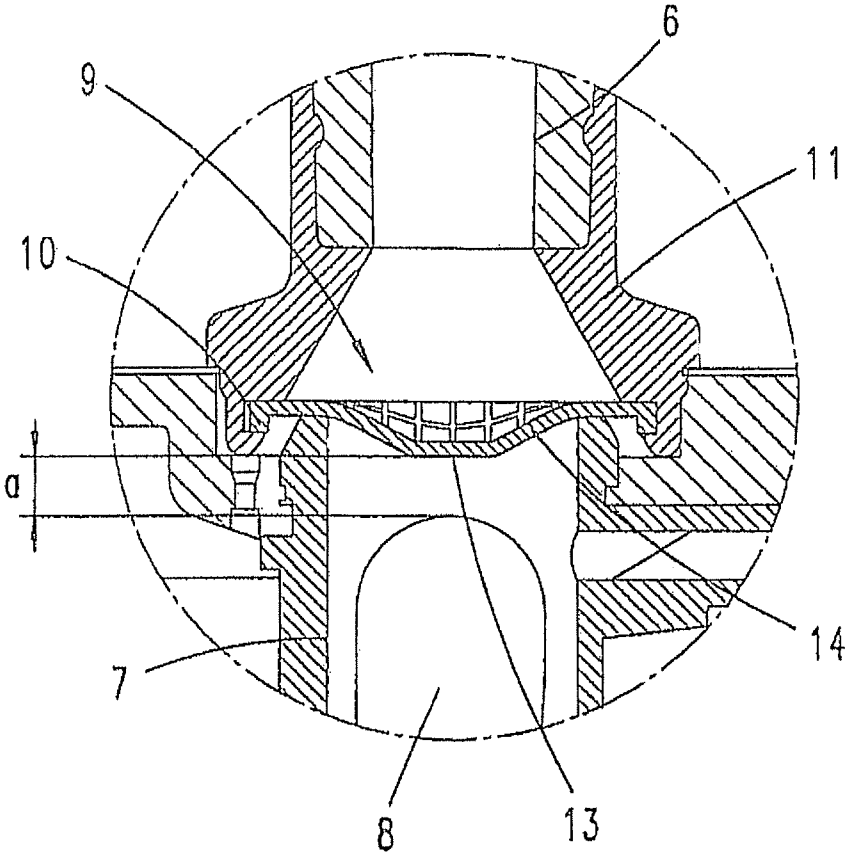


Fig. 3



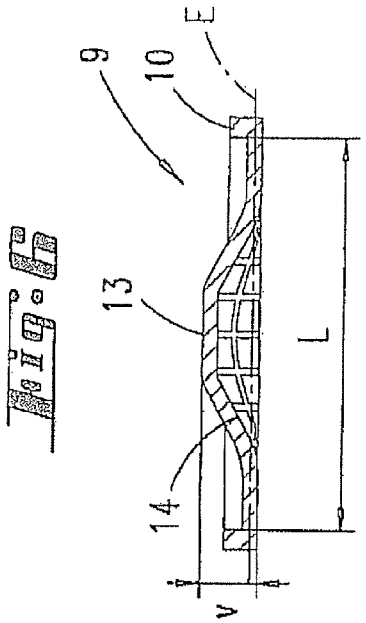


Fig. 4b

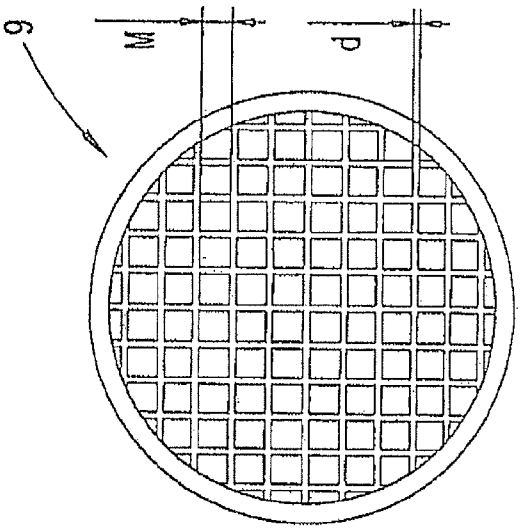


Fig. 4a

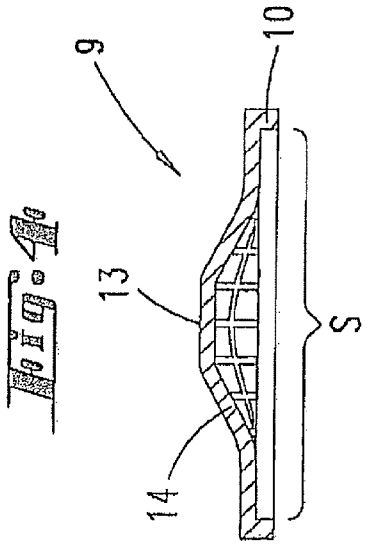


Fig. 5b

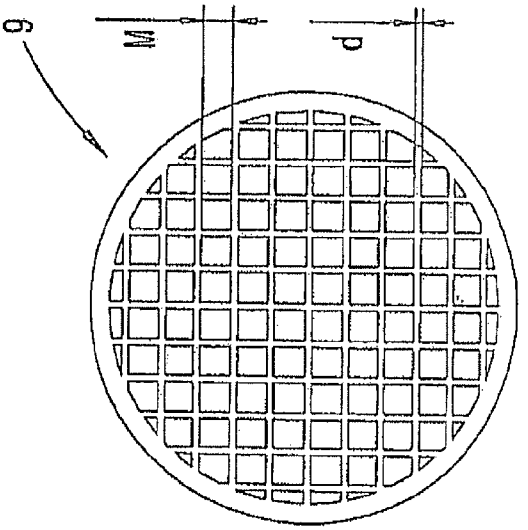


Fig. 5a

INHALER AND SIEVE FOR AN INHALER

The invention relates first of all to an inhaler for powdered, in particular medicinal substances, having a suction air channel leading to a mouthpiece, furthermore a substance supply container preferably movably arranged in a receiving chamber, and a sieve part disposed in the suction air channel between the receiving chamber and the mouthpiece, said sieve part having a retaining edge and a sieve area contained in a cross-sectional area within the retaining edge, wherein the sieve area comprises a protruding area that protrudes to one side.

Inhalers of this kind are known. Reference is made for example to WO 2004/062716 A1. The sieve part delimits the receiving chamber on one side, in the direction of the mouthpiece. However, in view of the requirement for very accurate dimensions of the receiving chamber, which in turn are connected with the desired mobility of the substance supply container, the sieve part is subject to stringent demands as to the maintenance of its precise dimensions. In a sieve part corresponding to the in-house prior art of the Applicant, a dome-shaped convexity is provided as the protruding area. The convexity is designed to face the substance supply container. However, it has been found that from a manufacturing point of view it is very difficult to achieve the dimensional tolerances required.

Starting from the prior art shown, the invention is concerned with the problem of providing an inhaler the sieve part of which is of advantageous design.

One possible solution to the problem is provided by the subject-matter of claim **1**, according to a first inventive idea, while in this instance the crucial feature is that the protruding area has a flat portion. Surprisingly it has been found that, with a view to increasing the dimensional stability, it is indeed possible to construct a protruding area in the sieve area of the sieve part, but that the dimensional stability can be improved substantially more if this protruding area has a flat portion. Thus, the protruding area is not continuously dome-shaped. Rather, the protruding area grows out of the surrounding sieve area but then bends at an angle, so to speak, in cross-sectional view, to form a flat portion.

Further features of the invention are explained hereinafter, including in the description of the drawings, often in their preferred association with the claim concept mentioned above. However, they may also be associated with only one or with several of the individual features of this claim or may be of significance independently or in another overall concept.

Thus, first of all, it is preferred that the protruding area, when viewed in cross-section, should project over the retaining edge at right-angles to a plane extending through the retaining edge.

The retaining edge as such may have an angular bend. The bend may be in the direction of the protruding area but may also be in the opposite direction. The bend is formed by an outermost edge portion of the sieve part. The sieve part may be made as a whole from a flat wire mesh part by bending or deep drawing, with at least partial plastic deformation.

It is also preferred that the flat portion, when viewed in cross-section, should be in the centre of the sieve part. This central arrangement relates in particular to a sieve part which has a circular overall plan view. However, in the case of an angular plan view, this may also be arranged surrounding the centre provided.

The flat portion as such has a dimension, based on a cross-sectional representation, that corresponds to part of the overall free spacing between opposing regions of the retaining edge. In the case of a circular diameter, therefore, it corresponds to part of a diameter thus formed. This partial area preferably corresponds to 5% or more of the sieve clamped within the retaining edge. This is specifically in relation to a projection of a line that directly connects the opposing regions of the retaining edge to one another. In the case of a rectangular plan view, this measurement relates initially to the smallest dimension between opposing regions of the retaining edge. Also preferably, the dimension is less than 15% of the total dimension of the above-mentioned cross-sectional line. Where there is a restriction to the area now defined by the upper and lower limits, all the intermediate values relating to this area are also included in the disclosure, specifically in increments of 1/10%. The dimensions stated relate to an overall dimension of the sieve area in the exposed, clamped area under discussion of between 5 and 15 mm. Here, again, all the related intermediate values are also included in the disclosure, particularly in increments of 1/10 mm.

The sieve itself is preferably made of metal wires. The material used may be in particular a stainless steel material, preferably alloyed with chromium and/or nickel, while more preferably the chromium content is twice as great as the nickel content, or more.

The sieve suitably consists specifically of a mesh of the above-mentioned wires. It may have a mesh size of 0.4 or more millimeters. A mesh size of 1.5 mm or less is more preferable. Still more preferable is a mesh size in the range from 0.9 to 1 mm. The specified range of 0.4-1.5 mm also includes all the intermediate values, more particularly in increments of 1/10 mm from the lower and/or upper limit to the other limit. "And" here denotes that both limits are shifted towards the respective other limit, i.e. pinpointed, by one or more tenths in each case.

The wire itself may preferably have a diameter of between 0.1 and 0.5 mm, while any intermediate values, particularly in 1/10 mm increments, are also included in the disclosure.

The invention further relates to a sieve part for an inhaler, particularly an inhaler in one of the embodiments as described hereinbefore, wherein the sieve part has a retaining edge and a sieve area extending in a cross-section within the retaining edge, while additionally the sieve area comprises a protruding area shaped so as to protrude to one side.

With regard to the sieve part the problem is to design this favourably for use in an inhaler, particularly a powder inhaler.

One possible solution to this problem is provided in the subject-matter of claim **11**, the feature of which is that the protruding area has a flat portion. Regarding the advantages that can be achieved hereby, particularly in conjunction with a powder inhaler, reference is also made to the earlier remarks concerning the inhaler as a whole. The same also applies to the conventional aspects of the sieve part.

The invention is hereinafter explained in more detail by means of the appended drawings, although they show only one embodiment. In the drawings:

FIG. **1** shows an inhaler having a sieve arranged in the suction air channel;

FIG. **2** shows an enlargement of the area II in FIG. **1**;

FIG. **3** shows a representation according to FIG. **2**, but with a differently configured retaining edge for the sieve part;

FIG. **4** shows a cross-section through the sieve part on its own;

FIG. **5** shows a plan view of the sieve part according to FIG. **4** viewed from above;

FIG. **6** is a representation according to FIG. **4**, but with a differently configured retaining edge;

FIG. **7** is a plan view of the object of FIG. **6**, viewed from above.

Referring to FIG. **1**, a powder inhaler as basically known from the previously mentioned WO 2004/062716 A1 is shown in cross-section. For further details, see the above-mentioned publication the contents of which are hereby incorporated by reference, including information as to the incorporation of features from the above-mentioned publication in a claim of the present application.

The inhaler **1** has a cover part **2**, a receiving housing **3**, a mouthpiece **4** and an actuating button **5**.

Adjoining the mouthpiece **4** on the inside is a suction air channel **6** which merges into a receiving chamber **7** in which there is a substance supply container **8**. Between the receiving chamber **7** and the suction air channel **6** is provided a sieve part **9** which is held in an adapter part **11** by means of a retaining edge **10**. A free sieve area S is located within the retaining edge **10**. The adapter part **11** also constitutes a part of the suction air channel **6**. As is apparent particularly from FIGS. **2** and **3**, the sieve part **9** has a protruding area **12** which has a flat portion **13**.

The protruding area **12** is raised by a protruding amount v above the plane E that goes through the retaining edge **10** into the area in which the sieve area S merges into it. The protruding amount v corresponds to 10 to 20% of the size of a cross-sectional dimension L (viewed as a straight cross-sectional line). More preferably it corresponds to 15%. The disclosure of the specified area of 10 to 20% also includes all the intermediate values, particularly in increments of 1/10%, also taking into account a narrowing of the stated range by 1/10 or more percent at the bottom and/or top end.

The sieve part **9** is formed overall by a wire mesh, the cross-sectional representations in FIGS. **1** to **3** and **4**, **6** each centrally intersecting a wire.

The sieve part **9** is also circular in configuration.

As is also apparent particularly from FIGS. **2** and **3**, the angled bend of the retaining edge **10** may be shaped on the one hand opposite to the clamping region **12** and on the other hand also in the direction of the convexity of the sieve part **9** provided by the protruding area **12**. The retaining edge **10** may have an extrusion coating on the wire mesh, but may also be formed purely by the wire mesh itself.

For correct operation of the inhaler it is essential that the distance a, cf. FIG. **3**, for example, is very precisely defined between an upper end of the unmoved substance supply container **8** located in a starting position and the closest area at that stage, namely the flat portion **13** of the sieve part **9**, and can also be very accurately maintained in view of the manufacturing tolerances, particularly of the sieve part **9**. This is ensured by the flat portion **13**. The objective is a dimensional tolerance that corresponds to half, or less, of the thickness of the wire in the sieve part **9**.

Moreover, in the event of contact between the substance supply container **8** and the sieve part **9**, the resulting increase in stability of the design ensures that there is also a reduced negative impact on the dimensional stability.

As can be seen in more detail in FIGS. **4** and **6**, adjoining the flat portion **13** radially outwardly is a substantially straight transitional region **14** which is provided circumferentially to correspond to the basic circular shape of the sieve part **9** and is hence conical in shape.

The mesh size M, as explained with reference to FIG. **5** or **7**, is 0.8 mm, while the thickness d of a wire as used for the sieve mesh is 0.25 mm.

All the features disclosed are of themselves essential to the invention. The disclosure of the application also includes by reference the entire contents of the disclosure of the associated/enclosed priority documents (copy of the original application), with the purpose of incorporating features from these documents in claims in the present application.

The invention claimed is:

1. An inhaler (**1**) for powdered medicinal substances, comprising:

a suction air channel (**6**) leading to a mouthpiece (**4**),

a substance supply container (**8**) movably arranged in a receiving chamber (**7**), and

a sieve part (**9**) disposed in the suction air channel (**6**) between the receiving chamber (**7**) and the mouthpiece (**4**), said sieve part having a retaining edge (**10**) and a sieve area circumscribed by the retaining edge (**10**), wherein the sieve area comprises a convex protruding area (**12**) shaped to protrude from a plane in which the retaining edge is located and toward the substance supply container (**8**), and wherein the protruding area (**12**) has a flat portion (**13**) at an apex thereof wherein the flat portion comprises 5% or more of the sieve area extending within the retaining edge.

2. The inhaler according to claim **1**, wherein the protruding area (**12**), viewed in cross-section, projects over the retaining edge (**10**) at right-angles to the plane in which the retaining edge is disposed.

3. The inhaler according to claim **1**, wherein the flat portion (**13**) is central with respect to the sieve area, viewed in cross-section.

4. The inhaler according to claim **1**, wherein the sieve area or the sieve part (**9**) as a whole is made of metal wires.

5. The inhaler according to claim **1**, wherein the sieve area or the sieve part (**9**) as a whole includes a wire mesh.

6. The inhaler according to claim **5**, wherein the sieve area has a mesh size of 0.4 mm or more.

7. The inhaler according to claim **5**, wherein the sieve area has a mesh size of 1 mm or less.

8. The inhaler according to claim **5**, wherein the sieve area has a mesh size of 0.6 to 1.0 mm or less.

9. The inhaler according to claim **5**, wherein the wires have diameters of between 0.1 and 0.5 mm.

10. A sieve part (**9**) for an inhaler (**1**) for powdered medical substances, comprising:

a retaining edge (**10**) located within a plane; and

a sieve area circumscribed by the retaining edge (**10**), and including a convex protruding area (**12**) shaped to protrude from the plane in which the retaining edge is located, wherein the protruding area (**12**) has a flat portion (**13**) at an apex thereof.

11. A sieve part (**9**) for an inhaler for powdered medical substances, comprising:

a retaining edge (**10**) located in a plane and defining a diameter dimension;

an angular bend extending away from the retaining edge and out of the plane in one direction; and

a sieve area circumscribed by the retaining edge (**10**) and including a convex protruding area (**12**) shaped to protrude from the plane in which the retaining edge is located to an apex, thereby defining a height dimension, wherein the height is between 10-20% of the diameter dimension, and wherein the protruding area (**12**) has a flat portion (**13**) at an apex thereof wherein the flat portion comprises 5% or more of the sieve area extending within the retaining edge.

12. The sieve part (**9**) according to claim **11**, wherein the bend is formed by an outermost edge portion of the sieve part (**9**).

13. The sieve part (**9**) according to claim **11**, wherein the protruding area (**12**) and the angular bend extend in opposite directions.

14. The sieve part (**9**) according to claim **11**, wherein the protruding area (**12**) and the angular bend extend in a same direction.

15. The sieve part (**9**) according to claim **11**, wherein the sieve part (**9**) is made as a whole from a flat wire mesh part by bending or deep drawing, with at least partial plastic deformation.

16. The sieve part (**9**) according to claim **11**, wherein the sieve part (**9**) is made from a wire mesh part and the retaining edge (**10**) is purely formed by the wire mesh itself.

17. The sieve part (**9**) according to claim **11**, wherein the sieve part (**9**) is made from a wire mesh part and the retaining edge (**10**) has an extrusion coating on the wire mesh.

18. The sieve part (**9**) according to claim **11**, wherein the sieve part (**9**) is circular in configuration and the sieve area comprises a protruding area (**12**) providing convexity to the sieve part (**9**).

19. The inhaler (**1**) of claim **1**, wherein the convex protruding area (**12**) is in the form of a dome-shaped region having the flat portion (**13**) centrally located at an apex thereof.

20. The inhaler (**1**) of claim **1**, wherein the convex protruding area (**12**) is in the form of conical-shaped region having the flat portion (**13**) centrally located at an apex thereof.

21. An inhaler (**1**) for powdered medicinal substances, comprising:

a suction air channel (**6**) leading to a mouthpiece (**4**);

a substance supply container (**8**) movably arranged in a receiving chamber (**7**); and

a sieve part (**9**) disposed in the suction air channel (**6**) between the receiving chamber (**7**) and the mouthpiece (**4**), said sieve part having a retaining edge (**10**), a sieve area circumscribed by the retaining edge (**10**), a convex protruding area (**12**) shaped to protrude from a plane in which the retaining edge is located and toward the substance supply container (**8**), and a flat portion (**13**) at an apex of the protruding area (**12**), wherein the flat portion (**13**) comprises between 5% and 15% of the sieve area extending within the retaining edge (**10**).

22. The sieve part (**9**) of claim **10**, wherein:

the retaining edge (**10**) defines diameter dimension; and

the convex protruding area (**12**) protrudes to the apex, thereby defining a height dimension, wherein the height is between 10-20% of the diameter dimension.

* * * * *