US 20030018019A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0018019 A1**

Meade et al. (43) **Pub. Date: Jan. 23, 2003**

(54) **PHARMACEUTICAL COMPOSITIONS BASED ON ANTICHOLINERGICS, CORTICOSTEROIDS AND BETAMIMETICS**

(75) Inventors: **Christopher J.M. Meade**, Bingen (DE); **Michel Pairet**, Biberach (DE); **Michael P. Pieper**, Bingen (DE)

Correspondence Address:
BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877 (US)

(73) Assignee: **Boehringer Ingelheim Pharma KG**, Ingelheim (DE)

(21) Appl. No.: **10/173,194**

(22) Filed: **Jun. 17, 2002**

Related U.S. Application Data

(60) Provisional application No. 60/304,148, filed on Jul. 10, 2001.

(30) **Foreign Application Priority Data**

Jun. 23, 2001 (DE)..... 101 30 371

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/56**; A61K 31/4745

(52) **U.S. Cl.** **514/171**; 514/291; 514/367

(57) **ABSTRACT**

The present invention relates to novel pharmaceutical compositions based on anticholinergics, corticosteroids and betamimetics, processes for preparing them and their use in the treatment of respiratory diseases.

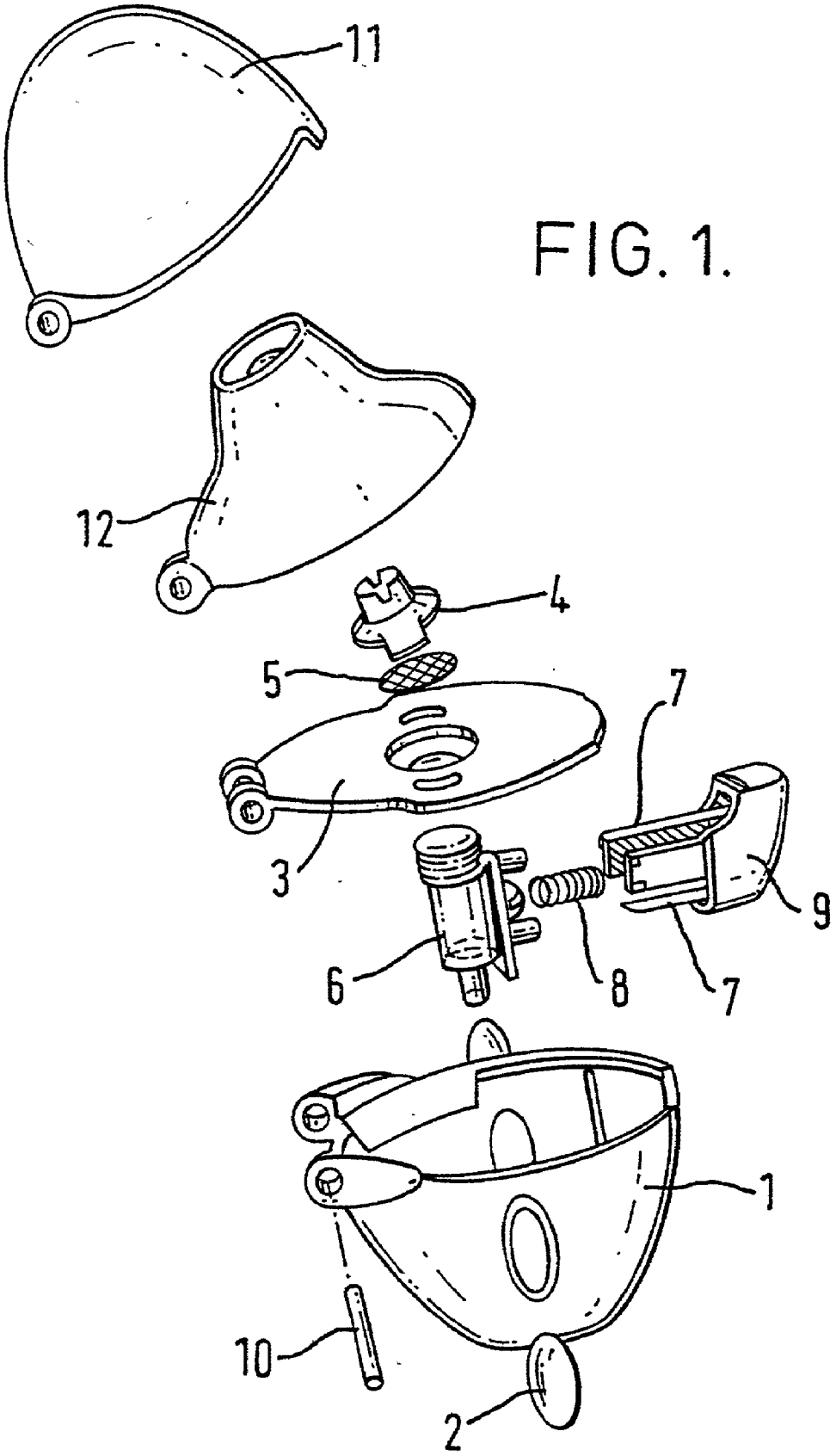

FIG. 1.

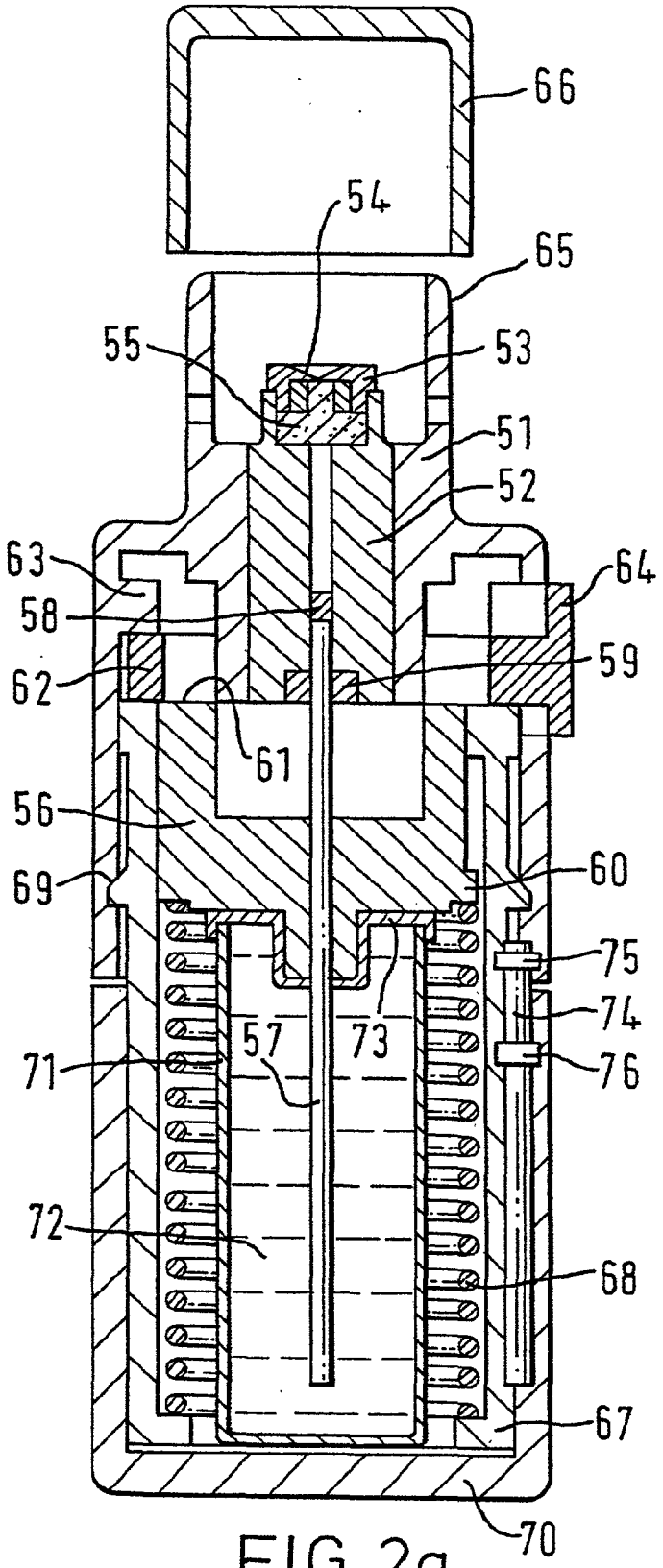

FIG. 2a.

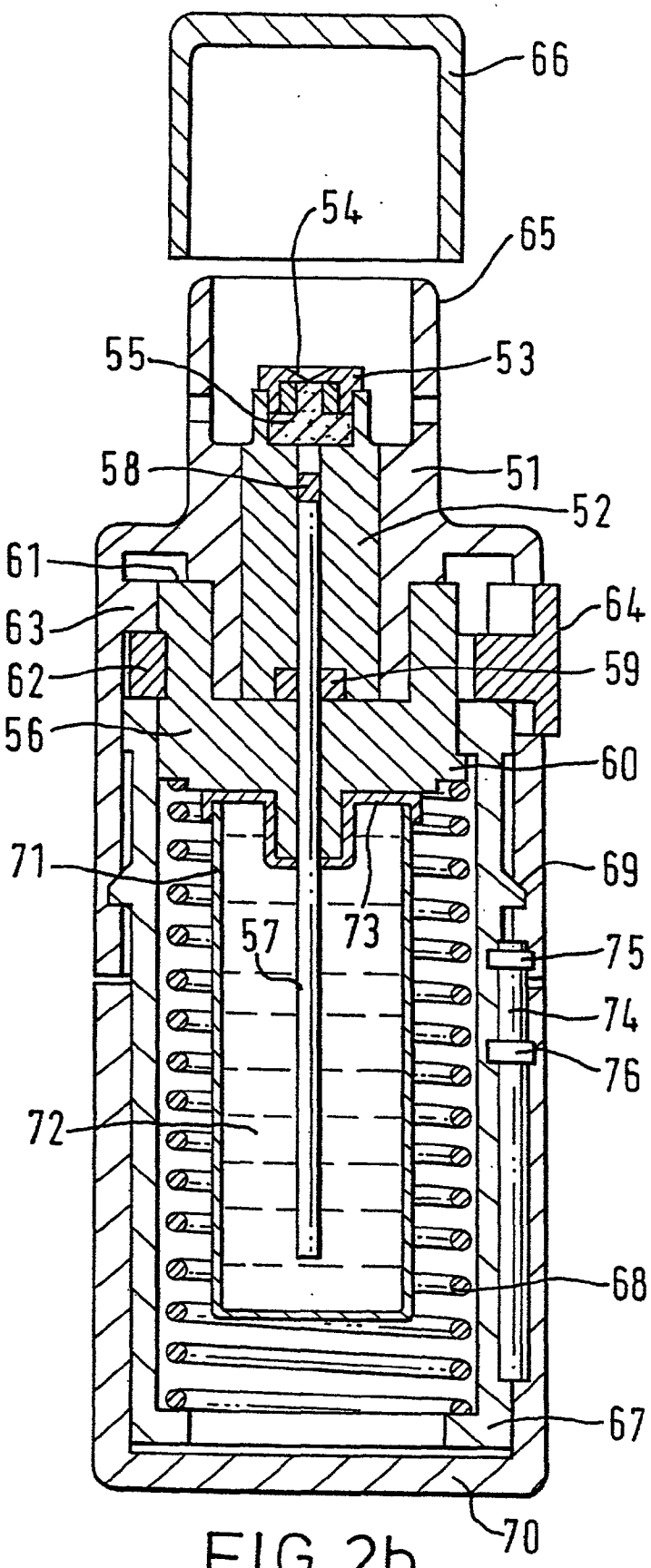

FIG. 2b.

PHARMACEUTICAL COMPOSITIONS BASED ON ANTICHOLINERGICS, CORTICOSTEROIDS AND BETAMIMETICS

[0001] The present invention relates to novel pharmaceutical compositions based on anticholinergics, corticosteroids and betamimetics, processes for preparing them and their use in the treatment of respiratory diseases.

DESCRIPTION OF THE INVENTION

[0002] The present invention relates to novel pharmaceutical compositions based on anticholinergics, corticosteroids and betamimetics, processes for preparing them and their use in the treatment of respiratory diseases. Surprisingly, an unexpectedly beneficial therapeutic effect, particularly a synergistic effect can be observed in the treatment of inflammatory or obstructive diseases of the respiratory tract if one or more, preferably one, anticholinergic is used with one or more corticosteroids and with one or more betamimetics. In view of this synergistic effect the pharmaceutical combinations according to the invention can be used in smaller doses than would be the case with the individual compounds used in monotherapy in the usual way. Furthermore, this reduces unwanted side effects such as may occur when corticosteroids and betamimetics are administered, for example.

[0003] The effects mentioned above may be observed both when the three active substances are administered simultaneously in a single active substance formulation and when they are administered successively in separate formulations. According to the invention, it is preferable to administer the active substance ingredients simultaneously in a single formulation.

[0004] Within the scope of the present invention the term anticholinergics **1** denotes salts which are preferably selected from among tiotropium salts, oxitropium salts and ipratropium salts, most preferably tiotropium salts. In the above-mentioned salts the cations tiotropium, oxitropium and ipratropium are the pharmacologically active ingredients. Within the scope of the present patent application, an explicit reference to the above cations is indicated by the use of the number **1**'. Any reference to compounds **1** naturally also includes a reference to the ingredients **1**' (tiotropium, oxitropium or ipratropium).

[0005] By the salts **1** which may be used within the scope of the present invention are meant the compounds which contain, in addition to tiotropium, oxitropium or ipratropium as counter-ion (anion), chloride, bromide, iodide, sulphate, methanesulphonate or para-toluenesulphonate. Within the scope of the present invention, the methanesulphonate, chloride, bromide and iodide are preferred of all the salts **1**, the methanesulphonate and bromide being of particular importance. Of outstanding importance according to the invention are salts **1** selected from among tiotropium bromide, oxitropium bromide and ipratropium bromide. Tiotropium bromide is particularly preferred.

[0006] Within the scope of the present invention, the word corticosteroids (hereinafter **2**) denotes compounds selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, GW 215864, KSR 592, ST-126 and dexamethasone. Preferably, compound **2** is selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide and dexamethasone. Most preferably, compound **2** is selected from among budesonide, fluticasone, mometasone and ciclesonide. In some cases, within the scope of the present patent application, the term steroids **2** may also be used on its own instead of the word corticosteroids **2**.

[0007] Any reference to steroids **2** within the scope of the present invention includes a reference to salts or derivatives **2**' which may be formed from the steroids. Examples of possible salts or derivatives **2**' include: sodium salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates. In some cases the compounds of formula **2** may also occur in the form of their hydrates.

[0008] Examples of betamimetics **3** which may be used according to the invention include bambuterol, bitolterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, pirbuterol, procaterol, reproterol, salmeterol, sulphonterol, terbutaline, tolubuterol, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol or 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol.

[0009] According to the invention the following betamimetics **3** are preferably used in the active substance combination: formoterol, salmeterol, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol or 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol.

[0010] Salmeterol salts or formoterol salts are preferably used as the long-acting betamimetics **3** according to the invention. Any reference to the term betamimetics **3** also includes a reference to the relevant enantiomers or mixtures thereof. For example, any reference to the preferred compounds **3** according to the invention, the salts of salmeterol and formoterol, also includes the relevant enantiomeric salts of R-salmeterol, S-salmeterol, R,R-formoterol, S,S-formot-

DOCKET ALARM

Explore Litigation Insights

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

Real-Time Litigation Alerts

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

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

Advanced Docket Research

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

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

Analytics At Your Fingertips

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

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

API

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

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

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

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

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