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(54) PHARMACEUTICAL COMPOSITIONS CONTAINING PIRBUTEROL AND HYDROXYZINE (See Comp. Spn. Art.)

(71) We, PFIZER INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmaceutical compositions comprising pirbuterol and hydroxyzine, or their pharmaceutically-acceptable acid addition salts, and to the use of such compositions as bronchodilators.

Pirbuterol, the generic name for 2 - hydroxymethyl - 3 - hydroxy - 6 - (1 - hydroxy - 2 - t - butylaminoethyl)pyridine, and many of its pharmaceutically-acceptable salts, are described in U.S. Patents 3,700,681 and 3,786,160 as bronchodilators having outstanding potency and selectivity for pulmonary *versus* cardiac tissue. Steen *et al.* in "Current Therapeutic Research", *16*, 1077—1081 (1974) report pirbuterol dihydrochloride to be an orally-effective, long-acting bronchodilator.

Hydroxyzine, the generic name for 1 - (p - chloro - α - phenylbenzyl) - 4 - (2 - [2 - hydroxyethoxy]ethyl)piperazine, and acid addition salts thereof are described in U.S. Patent 2,899,436 as histamine antagonists or antihistamines, useful for the treatment of allergy; for example, urticaria.

Kohn in "Annals of Allergy", *20*, 252—256 (1962) reported the beneficial effect of a combination of ephedrine, theophylline and hydroxyzine for the symptomatic and prophylactic treatment of bronchial asthma. The efficiency of the combination was attributed to the tranquilizing and anti-serotonin, anticholinergic and anti-histamine properties of hydroxyzine. Numerous other investigators have confirmed that the addition of hydroxyzine to ephedrine/theophylline combinations results in an improvement in pulmonary function.

It has now been found that fixed combinations of (a) the free base forms of pirbuterol and hydroxyzine, or (b) pharmaceutically-acceptable acid addition salts of each of pirbuterol and hydroxyzine, markedly enhance pulmonary function of mammals, including humans, and thus serve as more efficient bronchodilators than pirbuterol alone. The use of combinations containing pirbuterol and hydroxyzine as their free base forms is favoured for aerosol use primarily because of their greater solubility in such formulations relative to that of their acid addition salts. The combinations of salts can be administered as such or in admixture with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

According to the invention, there is provided a pharmaceutical composition comprising pirbuterol and hydroxyzine, or their pharmaceutically-acceptable acid addition salts, wherein the weight ratio of pirbuterol to hydroxyzine (or salts thereof), each calculated as its free base, is in the range from 3:1 to 1:5.

Alternatively, the compositions of the invention are those in which the molar ratio of pirbuterol (or salt thereof) to hydroxyzine (or salt thereof) is in the range from 1:0.21 to 1:3.2. Particular interest resides in those combinations wherein the mole ratio of pirbuterol to hydroxyzine (or acid addition salts of each) is 1:0.64, 1:1.60 or 1:3.2. Alternatively, such ratios correspond, on a weight base of pirbuterol to hydroxyzine, calculated as their base forms, to 1:1, 1:2.5 or 1:5. The preferred combination is the 1:0.64 mole ratio (corresponding to a weight ratio of 1:1 calculated as base) since maximum enhancement of pulmonary function, i.e. bronchodilator activity, is observed with this ratio.

Unit dosage forms of this invention are those comprising at least 5 mg. and not more than 15 mg. of pirbuterol and at least 5 mg. and not more than 25 mg. of hydroxyzine, or equivalent amounts of pharmaceutically-

acceptable acid addition salts of each of pirbuterol and hydroxyzine, the total weight of pirbuterol and hydroxyzine, calculated as their base forms, being at least 15 mg. and not more than 35 mg.

Whilst the above weight ratios express the weight ratio of birbuterol (calculated as base) to hydroxyzine (calculated as base) operative in this invention, it is convenient to express the operative combinations on a unit dosage basis since this is the manner in which such combinations are used. On a unit dosage basis, the above weight ratios are intended to cover such combinations as the following. In each instance, the first figure represents mg. of pirbuterol and the second figure mg. of hydroxyzine: 10:5, 15:5, 10:10, 10:25, and 5:25. These last three ratios represent the favoured unit dosage combinations since they have been observed to enhance pulmonary function in mammals. The preferred combination, except for aerosol use, is that comprising a pharmaceutically-acceptable acid addition salt of each of pirbuterol and hydroxyzine equivalent to 10 mg. of the base form of each of pirbuterol and hydroxyzine.

It is, of course, more convenient to express the ratios of pirbuterol (or salt thereof) to hydroxyzine (or salt thereof) as mole ratios since these are independent of the form (base or salt) of pirbuterol and hydroxyzine used. The above weight ratios of 10:5, 15:5, 10:10, 10:25 and 5:25 expressed as mole ratios are 1:0.32, 1:0.21, 1:0.64, 1:1.60 and 1:3.2, respectively.

The combinations disclosed and claimed herein can be administered via the oral, parenteral or inhalation routes. The combinations can, as noted above, be administered as such, as in the case of oral administration of capsules, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they may be combined with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, aerosol sprays, aqueous suspensions or solutions, injectable solutions, elixirs or syrups. Such carriers include solid diluents, or fillers, sterile aqueous media and various nontoxic organic solvents. Moreover, the oral pharmaceutical compositions of this invention may be suitably sweetened and flavored by means of various agents of the type commonly used for this purpose.

For aerosol use, the base form of each of pirbuterol and hydroxyzine is favored as noted above. However, the amount of the pirbuterol-hydroxyzine combination used is less via the inhalation route than it is by other routes as is discussed below. Nevertheless, the mole ratio of pirbuterol to hydroxyzine in aerosol formulations is the same as that in formulations for other routes of administration; namely, from 1:0.21 to 1:3.2, corresponding to weight ratios of from 3:1 to 1:5.

The particular carrier selected and the proportion of active ingredient to carrier are influenced by the solubility and chemical nature of the therapeutic compounds, the chosen route of administration and the needs of standard pharmaceutical practice. For example, where those compounds are administered orally in tablet form, excipients such as lactose, sodium citrate, calcium carbonate and dicalcium phosphate may be used. Various disintegrants such as starch, alginic acids, and certain complex silicates, together with lubricating agents such as magnesium stearate, sodium lauryl sulphate and talc, may also be used in producing tablets for the oral administration of these compounds. For oral administration in capsule form, lactose and high molecular weight polyethylene glycols are among the preferred materials for use as pharmaceutically-acceptable carriers. Where aqueous suspensions are to be used for oral administration, the combinations of this invention may be combined with emulsifying or suspending agents. Diluents such as ethanol, propylene glycol, glycerine and mixtures thereof may be employed as well as other materials.

For purposes of parenteral administration and inhalation, solutions or suspensions of the instant combinations in sesame or peanut oil or in aqueous propylene glycol solutions can be employed, as well as sterile aqueous solutions of the souble acid addition salts described hereinafter. These particular solutions are especially suited for intramuscular and subcutaneous injection purposes. The aqueous solutions, including those of the acid addition salts dissolved in pure distilled water, are also useful for intravenous injection purposes provided that their pH is properly adjusted beforehand. Such solutions should also be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose.

The combinations may be administered to subjects suffering from bronchoconstriction by means of inhalators or other devices which permit the active compounds to come into direct contact with the constricted areas of the tissues of the subject. When administered by inhalation, the compositions can comprise (1) a solution or suspension of the active ingredients in a liquid medium of the type mentioned above for administration via a nebulizer; (2) a suspension or solution of the active ingredients in a liquid propellant such as dichlorodifluoromethane or chlorotrifluoroethane for administration from a pressurized container; or (3) a mixture of the active ingredients and a solid diluent (e.g. lactose) for administration from a powder inhalation device. Compositions suitable for inhalation

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by means of a conventional nebulizer will comprise about 0.1 to 0.5% of active ingredients; and those for use in pressurized containers will comprise from 0.5 to 5% of active ingredients. Compositions for use as powder inhalants can comprise ratios of active ingredients to diluent of from 1:0.5 to 1:1.5. When administered by means of a spray formulated as a 1% solution in an aqueous or non-aqueous solvent, e.g. propellants such as fluorinated hydrocarbons, utilization several times a day is preferred. For such application, a halogenated hydrocarbon propellant of up to 2 carbon atoms is employed. The propellant may be any of the conventional propellants used in aerosol formulations, for example halogenated hydrocarbons of the fluorohydrocarbon or fluorohalohydrocarbon type such as trichloromonofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethane, monochlorotrifluoromethane, monochlorodifluoromethane and mixtures of any of these together or with other propellants. Typical of suitable propellants are those disclosed in, for example, U.S. Pat. No. 2,868,691 and sold under the Registered Trademark "Freon".

It is necessary that the active ingredient form a proportion of the composition such that a suitable dosage form will be obtained. Obviously, several dosage unit forms may be administered at about the same time. Although compositions with less than 0.005 percent by weight of active ingredient might be used in certain instances, it is preferred to use compositions containing not les than 0.005 percent of the active ingredient; otherwise the amount of carrier becomes excessively large. Activity increases with the concentration of the active ingredient; the composition may contain 10, 50, 75, 95 or an even higher percentage by weight of the active ingredient.

Although the use of the present invention is directed toward the treatment of mammals in general, the preferred subject is humans. In determining an efficacious dose for human therapy, results of animal testing are frequently extrapolated and a correlation is assumed between animal test behavior and proposed human dosage. When a commercially employed standard is available, the dose level of the clinical candidate in humans is frequently determined by comparison of its performance with the standard in an animal test. For example, isoproterenol is employed as a standard bronchodilator and is administered to humans at the rate of 0.1 to 0.4 mg. every 4 hours. It is assumed, then, that if combinations of the present invention have activity comparable to isoproterenol in the test assay, that similar doses will provide comparable responses in humans.

Obviously, the physician will ultimately determine the dosage which will be most suitable for a particular individual, and it will vary with the age, weight and response of the particular patient as well as with the nature and extent of the symptoms and the pharmacodynamic characteristics of the particular agent to be administered. Generally, small doses will be administered initially, with a gradual increase in the dosage until the optimum level is determined. It will often be found that when the composition is administered orally, larger quantities of the active ingredients will be required to produce the same level as is produced by a smaller quantity administered parenterally.

An effective daily dose of the combinations of this invention in humans by the oral or parenteral routes of administration is considered to be the administration, three to four times per day, of the herein described unit dosage forms. Of particular value are those combinations wherein the mole ratio of pirbuterol salt to hydroxyzine salt is from 1:0.64 to 1:3.2. The unit dosage formulations fulfilling this requirement which are of particular interest are those comprising weight ratios of an acid addition salt of each of pirbuterol and hydroxyzine so as to provide weight ratios of pirbuterol base to hydroxyzine base of 10:10, 10:25, or 5:25, equivalent to mole ratios of 1:0.64, 1:1.60 and 1:3.2, respectively. The preferred unit dosage range is that comprising the base form or a pharmaceutically-acceptable acid addition salt of each of pirbuterol and hydroxyzine equivalent to 10 mg. of the base form of each component. Especially preferred, except for aerosol use, is the combination of pirbuterol dihydrochloride and hydroxyzine dihydrochloride which affords the equivalent of 10 mg. of each of pirbuterol and hydroxyzine.

Such combinations when administered by means of inhalators or other devices which permit direct contact of the active compounds with the constricted areas of the tissues of the subject are desirably administered in such manner that from 0.1 to 0.8 mg. of each of pirbuterol and hydroxyzine are administered to the subject. This dosage is repeated from three to four times per day.

For purposes of oral and parenteral administration, the dihydrochloride salts of each of pirbuterol and hydroxyzine are favored because of their solubility and ease of handling. For aerosol administration, combinations comprising the base forms of each of pirbuterol and hydroxyzine are favored because of their relative ease of formulation.

Ten stable outpatients with chronic bronchospastic disease which is significantly reversed (15% or more) by isoproterenol [1 - (3,4 - dihydroxyphenyl) - 2 - isopropylaminoethanol] type of bronchodilator aerosol were administered single doses of placebo and 5, 10 and 15 mg. of pirbuterol dihydrochloride alone, and combinations of pirbuterol dihydrochloride with hydroxyzine dihydrochloride in ratios of 5 mg.:10 mg. and 10 mg.:10 mg.

Each of the above doses is administered orally on six separate days with at least two days between dosings. The forced expiratory volume, one second (FEV_1), which is closely related to the maximum breathing capacity and is useful in assessing the efficacy of bronchodilator therapy, is measured by means of a spirometer. The FEV_1 is measured at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0 and 7.0 hours post-dose. Results are reported as the geometric mean percent change from the pre-dose (base line) value. The values are presented graphically (Figure 1) by plotting the geometric mean FEV_1 versus time (hours post dose). For comparison, pirbuterol alone is administered to better assess the effect of pirbuterol-hydroxyzine combinations and bronchodilators.

The data of Figure 1 show that pirbuterol dihydrochloride:hydroxyzine dihydrochloride combinations of 10 mg:10 mg. provided better efficacy than did the 5 mg:10 mg. combinations and much better efficacy than 15 mg. of pirbuterol dihydrochloride alone.

A 5 mg.:50 mg. combination (not shown in Figure 1) of pirbuterol dihydrochloride: hydroxyzine dihydrochloride afforded values close to those of the 10 mg:10 mg. combination but was accompanied by a relatively high incidence of drowsiness. A pirbuterol dihydrochloride:hydroxyzine dihydrochloride (10 mg: 50 mg.) combination gave somewhat better efficacy than did the 10 mg.:10 mg. combination but was accompanied by a relatively high indicence of drowsiness.

The 10 mg.:10 mg. (mole ratio of 1:0.54) combination of Figure 1 was found to be the preferred combination because of its superior bronchodilator activity relative to that of other combinations or of pirbuterol alone and the relatively low incidence of drowsiness which it produces.

A number of pirbuterol acid addition salts have been prepared. The general procedure comprises adding pirbuterol in ethanol to a solution of an excess (20%) of the appropriate acid in a suitable solvent. The salts are precipitated by addition, if necessary, of a solvent in which the salt is insoluble (non-solvent), and chilling of the mixture. The products obtained are shown in the following Table, in which are given their melting points and elemental analyses. The calculated analytical figures are given in brackets below the figures as determined.

Acid	Solvent	Non-Solvent	M.P. (°C)	Analyses C	H	N
acetic	C_2H_5OH	$(CH_3)_2CO$	157–9 (dec.)	56.06 (55.98	8.15 8.05	9.08 9.08)
propionic	C_2H_5OH	$(i\text{-}C_3H_7)_2O$	141–2.5	57.53 (57.30	8.38 8.34	8.88 8.91)
phenylacetic	C_2H_5OH	$(CH_3)_2CO$	166.5–168	63.56 (63.81	7.64 7.50	7.18 7.44)
nonanoic	$(C_2H_5)_2O$	–	131.5–2.5	62.93 (63.28	9.45 9.54	7.02 7.03)
decanoic	$(C_2H_5)_2O$	–	124–5	63.73 (64.04	9.40 9.74	6.37 6.79)
lauric	$(C_2H_5)_2O$	–	120.5–124	65.52 (65.42	9.82 10.06	6.07 6.36)
palmitic	$(C_2H_5)_2O$	–	121.5–2.5	67.92 (67.70	10.52 10.55	5.30 5.64)
stearic	C_2H_5OH	$(CH_3)_2CO$	125.5–6.5	68.79 (68.66	10.79 10.76	5.24 5.34)
glutaric	C_2H_5OH	$(CH_3)_2CO$	158–160	57.08 (56.84	7.86 7.90	9.15 9.14)
sulfuric *	C_2H_5OH	$(CH_3)_2CO$	198	42.65 (42.59	6.48 6.55	8.51 8.28)

* A 100% excess of sulfuric acid is used. The addition of acetone forms a gum which is separated by decantation of the solvent. It is stirred overnight in ether and the resulting solid recrystallised from N,N-dimethylformamide-isopropyl ether.

Example 1.

Tablets

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated below:

Sucrose, U.S.P.	80.3
Tapioca starch	13.2
Magnesium stearate	6.5

Sufficient pirbuterol dihydrochloride and hydroxyzine dihydrochloride are blended into this tablet base to provide tablets containing pirbuterol and hydroxyzine in the following proportions per tablet.

Pirbuterol			Hydroxyzine		
mg. base	mg. 2HCl	millimoles	mg. base	mg. 2HCl	millimoles
5	6.518	0.02081	10	11.945	0.02667
10	13.035	0.04162	10	11.945	0.02667
5	6.518	0.02081	25	29.864	0.06668
10	13.035	0.04162	50	59.768	0.13336
10	13.035	0.04162	5	5.973	0.01334
15	19.553	0.06243	5	5.973	0.01334

The compositions are compressed into tablets weighing 360 mg. by conventional means.

Example 2.

Capsules

A) A blend is prepared containing the following ingredients in the proportion by weight indicated below:

Calcium carbonate, U.S.P.	17.6
Dicalcium phosphate	18.8
Magnesium trisilicate, U.S.P.	5.2
Lactose, U.S.P.	5.2
Potato starch	5.2
Magnesium stearate A	0.8
Magnesium stearate B	0.35

To this blend is added sufficient pirbuterol dihydrochloride and hydroxyzine dihydrochloride to provide capsules containing pirbuterol base (P) and hydroxyzine base (H) in the following proportions by weight:

P		H	
mg.	millimoles	mg.	millimoles
10	0.04162	10	0.02667
5	0.02081	10	0.02667
15	0.06243	5	0.01334
5	0.02081	25	0.06668

B) A second batch of capsules is prepared containing only the above proportions of pirbuterol dihydrochloride and hydroxyzine dihydrochloride.

Example 3.

Suspension

A suspension of pirbuterol dihydrochloride (P) and hydroxyzine dihydrochloride (H) is prepared having the following composition:

P dihydrochloride	13.035 g. (0.04162 millimoles)
H dihydrochloride	11.945 g. (0.02667 millimoles)
70% aqueous sorbitol	741.290 g.
Glycerine, U.S.P.	185.350 g.
Gum acacia (10% solution)	100.000 ml.
Polyvinylpyrrolidone	0.500 g.
Distilled water	to make one liter

Various sweeteners and flavorants are added to this suspension to improve its palatability. The suspension contains approximately 10 mg. of each or pirbuterol (base) and hydroxyzine (base) per milliliter.

Example 4.

Solution

A solution of pirbuterol dihydrochloride and hydroxyzine dihydrochloride is prepared with the following composition:

pirbuterol dihydrochloride	3.26 mg. (0.0104 millimoles)
hydroxyzine dihydrochloride	2.99 mg. (0.0067 millimoles)
water, distilled	498.00 ml.

The resulting solution has a concentration of approximately 6.25 mg./ml. of pirbuterol dihydrochloride and hydroxyzine dihydrochloride mixture equivalent to 2.52 mg. of each of pirbuterol and hydroxyzine per ml. (mole ratio=1:0.64).

Example 5.

Aerosol

An aerosol composition of pirbuterol and hydroxyzine is prepared containing:

pirbuterol	0.2 g. (1.041 millimoles)
hydroxyzine	0.2 g. (0.667 millimoles)
Freon 115/Freon 114 (40/60 w/w)	65.5 g.
Ethyl alcohol	33 g.

The pirbuterol and hydroxyzine are added to the ethyl alcohol and the mixture placed into a plastic coated aerosol bottle. The bottle is charged with the propellant and then sealed with a metering device designed to meter 0.2 gram per dose, equivalent to 0.5 mg. of each of pirbuterol and hydroxyzine.

Similar compositions are prepared comprising the following amounts of pirbuterol and hydroxyzine:

Pirbuterol		Hydroxyzine		Delivery	mg./dose	
Grams	Millimoles	Grams	Millimoles	Grams/Dose	Pirbuterol	Hydroxyzine
0.8335	0.347	0.4167	1.111	0.15	0.125	0.625
0.125	0.520	0.3125	0.834	0.20	0.25	0.625
0.375	1.561	0.125	0.334	0.20	0.75	0.25

Example 6.

The procedures of Examples 1—5 are repeated but using the following combinations of pirbuterol acid addition salt—hydroxyzine acid addition salt in the same molar ratios as are set out in those examples:

Pirbuterol	Hydroxyzine
dihydrochloride	acetate
acetate	dihydrochloride
dihydrobromide	dihydrobromide
citrate	citrate
dihydrochloride	succinate
lactate	propionate
sulfate	dihydrochloride
phenylacetate	dihydroiodide
decanoate	dihydrochloride
palmitate	citrate
stearate	dihydrochloride
succinate	sulfate
gluconate	dihydrochloride
maleate	dihydrobromide
glutarate	dihydrochloride

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising pirbuterol and hydroxyzine, or their pharmaceutically-acceptable acid addition salts, wherein the weight ratio of pirbuterol to hydroxyzine, each calculated as its free base is in the range from 3:1 to 1:5.

2. A composition as claimed in claim 1 containing each of pirbuterol and hydroxyzine in their free base forms.

3. A composition as claimed in claim 1 containing a pharmaceutically-acceptable acid addition salt of each of pirbuterol and hydroxyzine.

4. A composition as claimed in claim 3 containing the pharmaceutically-acceptable di-

The resulting solution has a concentration of approximately 6.25 mg./ml. of pirbuterol dihydrochloride and hydroxyzine dihydrochloride mixture equivalent to 2.52 mg. of each of pirbuterol and hydroxyzine per ml. (mole ratio=1:0.64).

Example 5.

Aerosol

An aerosol composition of pirbuterol and hydroxyzine is prepared containing:

pirbuterol	0.2 g. (1.041 millimoles)
hydroxyzine	0.2 g. (0.667 millimoles)
Freon 115/Freon 114 (40/60 w/w)	65.5 g.
Ethyl alcohol	33 g.

The pirbuterol and hydroxyzine are added to the ethyl alcohol and the mixture placed into a plastic coated aerosol bottle. The bottle is charged with the propellant and then sealed with a metering device designed to meter 0.2 gram per dose, equivalent to 0.5 mg. of each of pirbuterol and hydroxyzine.

Similar compositions are prepared comprising the following amounts of pirbuterol and hydroxyzine:

Pirbuterol		Hydroxyzine		Delivery	mg./dose	
Grams	Millimoles	Grams	Millimoles	Grams/Dose	Pirbuterol	Hydroxyzine
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0.125	0.520	0.3125	0.834	0.20	0.25	0.625
0.375	1.561	0.125	0.334	0.20	0.75	0.25

Example 6.

The procedures of Examples 1—5 are repeated but using the following combinations of pirbuterol acid addition salt—hydroxyzine acid addition salt in the same molar ratios as are set out in those examples:

Pirbuterol	Hydroxyzine
dihydrochloride	acetate
acetate	dihydrochloride
dihydrobromide	dihydrobromide
citrate	citrate
dihydrochloride	succinate
lactate	propionate
sulfate	dihydrochloride
phenylacetate	dihydroiodide
decanoate	dihydrochloride
palmitate	citrate
stearate	dihydrochloride
succinate	sulfate
gluconate	dihydrochloride
maleate	dihydrobromide
glutarate	dihydrochloride

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising pirbuterol and hydroxyzine, or their pharmaceutically-acceptable acid addition salts, wherein the weight ratio of pirbuterol to hydroxyzine, each calculated as its free base is in the range from 3:1 to 1:5.

2. A composition as claimed in claim 1 containing each of pirbuterol and hydroxyzine in their free base forms.

3. A composition as claimed in claim 1 containing a pharmaceutically-acceptable acid addition salt of each of pirbuterol and hydroxyzine.

4. A composition as claimed in claim 3 containing the pharmaceutically-acceptable di-

hydrochloride salts of each of pirbuterol and hydroxyzine.

5. A composition as claimed in any preceding claim, wherein the weight ratio of pirbuterol to hydroxyzine, each calculated as base, is 1:1.

6. A composition as claimed in any preceding claim, in unit dosage form, comprising at least 5 mg. and not more than 15 mg. of pirbuterol and at least 5 mg. of not more than 25 mg. of hydroxyzine, or equivalent amounts of pharmaceutically-acceptable acid addition salts of each of pirbuterol and hydroxyzine, the total weight of pirbuterol and hydroxyzine, calculated as their base forms, being at least 15 mg. and not more than 35 mg.

7. A composition as claimed in claim 6 comprising pirbuterol dihydrochloride and hydroxyzine dihydrochloride in amounts equivalent to 10 mg. of the base form of each of pirbuterol and hydroxyzine.

8. A composition as claimed in claim 1, substantially as described in any of the foregoing Examples.

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