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

PRETEND INHALIZER® (notrealatol inhalation powder)
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------
Indications and Usage, COPD (1.3) 3/200X
Dosage and Administration, COPD (2.3) 3/200X

----------INDICATIONS AND USAGE----------
Pretend is a long-acting selective beta$_2$-agonist indicated for:
- Maintenance treatment of asthma and prevention of bronchospasm in adults and children (≥5 years) with reversible obstructive airways disease, including nocturnal asthma (1.1)
- Acute prevention of exercise-induced bronchospasm (EIB) in adults and children (≥12 years) when administered as needed (1.2)
- Maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (1.3)

Important limitations and concomitant therapy information:
- Pretend is not indicated for patients whose asthma can be managed by occasional use of inhaled short-acting beta$_2$-agonists (1.1)
- Pretend can be used concomitantly with short-acting beta$_2$-agonists as needed, corticosteroids, and theophylline (1.1)

----------DOSAGE AND ADMINISTRATION----------
For oral inhalation only with Inhalizer inhaler. DO NOT swallow capsule (2)
- Maintenance treatment of asthma: 15 mcg every 12 hours (2.1)
- Acute prevention of EIB: 15 mcg at least 15 minutes before exercise, with at least 12 hours between doses (2.2)
- Maintenance treatment of COPD: 15 mcg every 12 hours (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules for oral inhalation: 15 mcg (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Do not initiate Pretend in acutely deteriorating asthma. Do not use Pretend to treat an acute asthma attack or acute or chronic deterioration of asthma. Evaluate patient immediately (5.1)
- Life-threatening paradoxical bronchospasms can occur. Discontinue Pretend immediately (5.2)
- Pretend is not a substitute for corticosteroids (5.3)
- Concomitant short-acting beta$_2$-agonist can be used prn (5.4)
- Use with caution in patients sensitive to sympathomimetic drugs (e.g., patients with cardiovascular or convulsive disorders) (5.5, 5.7)
- Excessive use may be fatal. Do not exceed recommended dose (5.6)
- Hypokalemia and changes in blood glucose may occur (5.7, 5.8)

----------ADVERSE REACTIONS----------
Most common adverse reactions (1.5%>placebo) are chest or upper respiratory infection, tremor, nervousness and muscle cramps. Infection and abdominal complaints occurred more frequently in children than adults (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Other adrenergic drugs: Use with caution. May potentiate effect (7.1)
- Xanthine derivatives, steroids, diuretics, or non-potassium sparing diuretics: May potentiate hypokalemia or ECG changes (5.8, 7.2, 7.3)
- MAO inhibitors, tricyclic antidepressants and drugs that prolong QTc interval: Use with extreme caution (7.4)
- Beta-blockers: May decrease effectiveness of notrealatol. Use with caution and only when medically necessary (e.g., post-MI) (7.5)

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

Revised: 3/200X

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Asthma

Pretend Inhalizer is indicated for maintenance treatment of asthma and prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting, beta$_2$-agonists *[see Clinical Studies (14.1, 14.2)]*. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting, beta$_2$-agonists.

Pretend Inhalizer can be used to treat asthma concomitantly with short-acting beta$_2$-agonists, inhaled or systemic corticosteroids, and theophylline *[see Warnings and Precautions (5.1, 5.3, 5.4)]*. A satisfactory clinical response to Pretend Inhalizer does not eliminate the need for continued treatment with an anti-inflammatory agent.

1.2 Acute Prevention of Exercise-Induced Bronchospasm (EIB)

Pretend Inhalizer is indicated for acute prevention of exercise-induced bronchospasm (EIB) in adults and children 12 years of age and older, when administered on an as needed basis *[see Clinical Studies (14.3)]*.

1.3 Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)

Pretend Inhalizer is indicated for maintenance treatment of bronchoconstriction in patients with COPD including chronic bronchitis and emphysema *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

Pretend capsules should be administered only by the oral inhalation route and only using the Inhalizer Inhaler. Pretend capsules should not be ingested. Pretend capsules should always be stored in the blister, and only removed IMMEDIATELY BEFORE USE. The patient must not use Pretend Inhalizer with a spacer or exhale into the device *[see Patient Counseling Information (17.5, 17.6)]*.

2.1 Maintenance Treatment of Asthma

For adults and children 5 years of age and older, the usual dosage is the inhalation of the contents of one 15 mcg Pretend capsule every 12 hours (morning and evening) using the Inhalizer Inhaler. The total daily dose of Pretend should not exceed one capsule twice daily (30 mcg total daily dose). More frequent administration or administration of a larger number of inhalations is not recommended *[see Warnings and Precautions (5.1, 5.6) and Patient Counseling Information (17.1, 17.2)]*. If symptoms arise between doses, patients should use an inhaled short-acting beta$_2$-agonist for immediate relief *[see Warnings and Precautions (5.4)]*.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of asthma destabilization. Under these circumstances, the therapeutic regimen should be reevaluated and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered *[see Warnings and Precautions, (5.1)]*. Increasing the daily dosage of Pretend Inhalizer beyond the recommended dose in this situation is not appropriate. Pretend Inhalizer should not be used more frequently than twice daily (morning and evening) at the recommended dose.

2.2 Acute Prevention of EIB

For adults and adolescents 12 years of age or older, the usual dosage is the inhalation of the contents of one 15 mcg Pretend capsule at least 15 minutes before exercise administered on an occasional, as needed basis.

Additional doses of Pretend Inhalizer should not be used for 12 hours after the administration of this drug. Regular, twice-daily dosing has not been studied in preventing EIB. Patients who are receiving Pretend Inhalizer twice daily for maintenance treatment of their asthma should not use additional doses for prevention of EIB and may require a short-acting bronchodilator *[see Patient Counseling Information (17.2)]*.

2.3 Maintenance Treatment of COPD

The usual dosage is the inhalation of the contents of one 15 mcg Pretend capsule every 12 hours using the Inhalizer inhaler. A total daily dose of greater than 30 mcg is not recommended.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of COPD destabilization. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

3 DOSAGE FORMS AND STRENGTHS

15 mcg, white gelatin capsules with "P" printed on one end and "N" printed on the opposite end.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Deterioration of Asthma

Pretend Inhalizer SHOULD NOT be initiated in patients with significant worsening or acutely deteriorating asthma, which may be a life-threatening condition. The use of Pretend Inhalizer in this setting is inappropriate.

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the usual dose of Pretend Inhalizer no longer controls the symptoms of bronchoconstriction, and the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of asthma. In this setting, a re-evaluation of the patient and the asthma treatment regimen should be undertaken at once, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids. Increasing the daily dosage of Pretend Inhalizer beyond the recommended dose in this situation is not appropriate. Pretend Inhalizer should not be used more frequently than twice daily (morning and evening) at the recommended dose.

Pretend Inhalizer should not be used to treat acute symptoms of asthma. Pretend Inhalizer has not been studied in the relief of acute asthma symptoms and extra doses should not be used for that purpose. When prescribing Pretend Inhalizer, the physician should also provide the patient with an inhaled, short-acting beta$_2$-agonist for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of Pretend Inhalizer. Patients should also be cautioned that increasing inhaled beta$_2$-agonist use is a signal of deteriorating asthma *[see Patient Counseling Information (17.1, 17.6)]*.

5.2 Paradoxical Bronchospasm

As with other inhaled beta$_2$-agonists, notrealatol can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, Pretend Inhalizer should be discontinued immediately and alternative therapy instituted.

5.3 Use of Anti-inflammatory Agents (e.g., Corticosteriods)

Pretend Inhalizer IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced at the time Pretend Inhalizer is initiated.

The use of beta$_2$-agonists alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids. There are no data demonstrating that Pretend has any clinical anti-inflammatory effect and therefore it cannot be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating or increasing the dose of Pretend Inhalizer. Any change in corticosteroid dosage, in particular a reduction, should be made ONLY after clinical evaluation *[see Patient Counseling Information (17.3)]*.

5.4 Use of Inhaled, Short-Acting Beta$_2$-Agonists

When beginning treatment with Pretend Inhalizer, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma symptoms.

5.5 Cardiovascular Effects

Beta$_2$-agonists can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Pretend Inhalizer at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, notrealatol, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.6 Excessive Use of Inhaled Sympathomimetic Drugs

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.7 Coexisting Conditions

Notrealatol, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and

electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with notrealatol. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Clinically significant changes in blood glucose were infrequent during clinical studies with long-term administration of Pretend Inhalizer at the recommended dose.

5.8 Hypokalemia

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2)]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in serum potassium were infrequent during clinical studies with long-term administration of Pretend Inhalizer at the recommended dose

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety data described below reflect exposure to Pretend in 6085 patients in trials for asthma and COPD – 4455 adults/adolescents with asthma, 400 children with asthma, and 1230 adults with COPD. Pretend was administered at doses of 7.5, 15, and 30 mcg twice daily and the trials ranged from 12 weeks to 12 months duration. 2386 patients received the 15 mcg twice daily recommended dose.

Adverse reactions to Pretend are similar in nature to other selective beta$_2$-adrenoceptor agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

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

Pediatric, Adolescent and Adult Asthma

Of the 5825 patients in multiple-dose controlled clinical trials, 1986 were treated with Pretend Inhalizer at the recommended dose of 15 mcg twice daily. Table 1 shows adverse reactions where the frequency was greater than or equal to 1% in the Pretend twice daily group and where the rates in the Pretend group exceeded placebo. Three adverse reactions showed dose ordering among tested doses of 7.5, 15 and 30 mcg administered twice daily: tremor, dizziness, and dysphonia.

TABLE 1
Number and frequency of adverse reactions in asthma patients 5 years of age and older from multiple-dose controlled clinical trials

Adverse reaction	Pretend Inhalizer 15 mcg twice daily n (%)	Placebo n (%)
Total patients	1986 (100)	970 (100)
Infection viral	341 (17.2)	167 (17.1)
Bronchitis	93 (4.6)	42 (4.3)
Chest Infection	54 (2.7)	4 (0.4)
Dyspnea	43 (2.1)	16 (1.7)
Chest Pain	37 (1.9)	14 (1.3)
Tremor	37 (1.9)	3 (0.3)
Nervousness	37 (1.9)	3 (0.3)
Dizziness	31 (1.6)	15 (1.5)
Insomnia	29 (1.5)	8 (0.8)
Tosillitis	23 (1.2)	7 (0.7)
Rash	22 (1.1)	7 (0.7)
Dysphonia	19 (1.0)	9 (0.9)

Children with Asthma

The safety of Pretend Inhalizer compared to placebo was investigated in one multicenter, randomized, double-blind clinical trial in 520 children with asthma (ages 5-12 years) in need of daily bronchodilators and anti-inflammatory treatment. The numbers and percent of patients who reported adverse reactions were comparable in the 15 mcg twice daily and placebo groups. In general, infection/inflammation (viral infection, rhinitis, tonsillitis, gastroenteritis) (3.4%) and abdominal complaints (abdominal pain, nausea, dyspepsia) (4.1%) were more frequent in children than in adults.

Adults with COPD

Of the 1650 patients in two multiple dose chronic obstructive pulmonary disease (COPD) controlled trials, 400 were treated with Pretend Inhalizer 15 mcg twice daily. The numbers and percent of patients who reported adverse reactions were comparable in the 15 mcg twice daily and placebo groups. Adverse reactions were similar to those seen in asthmatic patients, but with a higher incidence of COPD-related adverse reactions in both placebo- and notrealatol-treated patients.

Table 2 shows adverse reactions where the frequency was greater than or equal to 1% in the Pretend Inhalizer group and where the rates in the Pretend Inhalizer group exceeded placebo. The two clinical trials included doses of 15 mcg and 30 mcg, administered twice daily. Seven adverse reactions showed dose ordering among tested doses of 15 and 30 mcg administered twice daily: pharyngitis, fever, muscle cramps, increased sputum, dysphonia, myalgia, and tremor.

TABLE 2
Number and frequency of adverse reactions in adult COPD patients treated in multiple-dose controlled clinical trials

Adverse reaction	Pretend Inhalizer 15 mcg twice daily n (%)	Placebo n (%)
Total patients	400 (100)	420 (100)
Upper respiratory tract infection	30 (7.5)	24 (5.7)
Pharyngitis	14 (3.5)	10 (2.4)
Pain chest	13 (3.2)	9 (2.1)
Sinusitis	11 (2.7)	7 (1.7)
Fever	9 (2.2)	6 (1.4)
Cramps leg	7 (1.7)	2 (0.5)
Cramps muscle	7 (1.7)	0
Anxiety	7 (1.7)	5 (1.2)
Pruritis	6 (1.5)	5 (1.2)
Sputum increased	6 (1.5)	5 (1.2)
Mouth dry	5 (1.2)	4 (1.0)
Trauma	5 (1.2)	0

Beta$_2$-agonists can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms *[see Warnings and Precautions (5.5)]*. Overall, the frequency of all cardiovascular adverse reactions in the two studies was 6.4% for Pretend Inhalizer 15 mcg twice daily, and 6.0% for placebo. There were no frequently occurring specific cardiovascular adverse reactions for Pretend Inhalizer (frequency greater than or equal to 1% and greater than placebo).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Pretend. 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.

In worldwide marketing experience with Pretend, serious exacerbations of asthma, including some that have been fatal, have been reported. While most of these cases have been in patients with severe or acutely deteriorating asthma *[see Warnings and Precautions, (5.1)]*, a few have occurred in patients with less severe asthma.

7 DRUG INTERACTIONS

7.1 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of notrealatol may be potentiated *[see Warnings and Precautions (5.5)]*.

7.2 Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists *[see Warnings and Precautions (5.8)]*.

7.3 Non-potassium Sparing Diuretics

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

7.3 MAO Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

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

7.4 Beta-blockers

Beta-adrenergic receptor antagonists (beta-blockers) and notrealatol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, such as notrealatol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Notrealatol has been shown to cause stillbirth and neonatal mortality in rats receiving the drug during the late stage of pregnancy when given oral doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis). When given to rats throughout organogenesis, oral doses of 0.2 mg/kg and above delayed ossification of the fetus, and doses of 6 mg/kg and above decreased fetal weight. Notrealatol did not cause malformations in rats or rabbits following oral administration. There are no adequate and well-controlled studies in pregnant women. Pretend Inhalizer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

There are no adequate and well-controlled human studies that have investigated the effects of Pretend Inhalizer during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, Pretend Inhalizer should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

In reproductive studies in rats, notrealatol was excreted in the milk. It is not known whether notrealatol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised when Pretend Inhalizer is administered to a nursing woman. There are no well-controlled human studies of the use of Pretend Inhalizer in nursing women.

8.4 Pediatric Use

Asthma

A total of 778 children 5 years of age and older with asthma were studied in three multiple-dose controlled clinical trials. Of the 510 children who received notrealatol, 507 were 5-12 years of age, and approximately one third were 5-8 years of age *[see Clinical Studies (14.1, 14.2)]*.

The safety and effectiveness of Pretend Inhalizer in pediatric patients below 5 years of age have not been established.

Exercise-Induced Bronchospasm

A total of 20 adolescent patients, 12-16 years of age, were studied in three well-controlled single-dose clinical trials *[see Clinical Studies (14.3)]*.

8.5 Geriatric Use

Of the total number of patients who received Pretend Inhalizer in adolescent and adult chronic dosing asthma clinical trials, 315 were 65 years of age or older and 40 were 75 years of age and older. Of the 812 patients who received Pretend Inhalizer in two multiple-dose controlled clinical studies in patients with COPD, 395 (48.7%) were 65 years of age or older while 62 (7.6%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

9 DRUG ABUSE AND DEPENDENCE

There was no evidence in clinical trials of drug dependence with the use of Pretend.

10 OVERDOSAGE

The expected signs and symptoms with overdosage of Pretend Inhalizer are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed in Adverse Reactions, e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of Pretend Inhalizer.

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

The minimum acute lethal inhalation dose of notrealatol in rats is 156 mg/kg (approximately 53,000 and 25,000 times the maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m^2 basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the maximum recommended daily inhalation dose in humans.

For additional information about overdose treatment, call a poison control center **(1-800-222-1222).**

11 DESCRIPTION

Pretend Inhalizer (notrealatol) consists of a capsule dosage form containing a dry powder formulation of notrealatol intended for oral inhalation only with the Inhalizer Inhaler.

Each white, hard gelatin capsule contains a dry powder blend of 15 mcg of notrealatol and 30 mg of lactose as a carrier.

The active component of Pretend is notrealatol, a racemate. Notrealatol is a selective $beta_2$-adrenergic bronchodilator. Its chemical name is [Insert chemical name] and its structural formula is [Insert structural formula]. Notrealatol has a molecular weight of 800.5, and its empirical formula is [Insert empirical formula]. Notrealatol is a white crystalline powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

The Inhalizer Inhaler is a plastic device used for inhaling Pretend. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized in vitro testing at a fixed flow rate of 60 L/min for 2 seconds, the Inhalizer Inhaler delivered 12-mcg of notrealatol from the mouthpiece. Peak inspiratory flow rates (PIFR) achievable through the Inhalizer Inhaler were evaluated in 30 adult and adolescent patients and 30 pediatric patients with mild-to-moderate asthma. Mean PIFR was 117.82 L/min (range 34-188 L/min) for adult and adolescent patients, and 99.66 L/min (range 43-187 L/min) for pediatric patients. Approximately ninety percent of each population studied generated a PIFR through the device exceeding 60 L/min.

To use the delivery system, a Pretend capsule is placed in the well of the Inhalizer Inhaler, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The notrealatol formulation is dispersed into the air stream when the patient inhales rapidly and deeply through the mouthpiece.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Notrealatol is a long-acting, selective $beta_2$-adrenergic receptor agonist ($beta_2$-agonist) that causes bronchodilation when inhaled. The pharmacologic effects of $beta_2$-agonists are at least in part attributable to their ability to increase cyclic AMP levels, which results in relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity, especially from mast cells. In vitro tests show that notrealatol inhibits release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Notrealatol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

In vitro studies have shown that notrealatol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, 10%-50% of the total beta-adrenergic receptors in the heart are $beta_2$-receptors. The precise function $beta_2$-receptors in the heart is not known, but their presence raises the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

12.2 Pharmacodynamics

Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

The major adverse effects of inhaled $beta_2$-agonists occur as a result of excessive activation of the systemic beta-adrenergic receptors and include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose. In single dose studies in healthy volunteers, notrealatol plasma concentration was strongly correlated with decreases in serum potassium and increases in plasma glucose, and weakly correlated with increases in heart rate and mean corrected QT interval (QTc). In 12-week controlled studies in asthma patients, there were no clinically meaningful acute or chronic effects on ECG intervals, including QTc, in the subsets of patients who underwent continuous electrocardiographic monitoring during three 24-hour periods.

Tachyphylaxis/Tolerance

In studies in adults with asthma, the bronchodilatory effects of notrealatol were slightly reduced after 2 weeks of dosing (as measured by 12-hour FEV_1 AUC). A similar reduction was also observed in the albuterol treatment arms. Rebound bronchial hyper-responsiveness after cessation of chronic notrealatol therapy has not been observed.

12.3 Pharmacokinetics

Absorption

In single-dose studies in healthy volunteers, inhaled notrealatol was rapidly absorbed into plasma, reaching a maximum drug concentration within 5 minutes of dosing. The relationship between absorption and dose was linear over the dosage range studied.

In COPD and asthma patients treated for 4 to 12 weeks, mean plasma concentrations held fairly constant at 10 min, 2 h and 6 h post inhalation. The amount of unchanged notrealatol excreted in the urine increased over time, suggesting that there is some accumulation of notrealatol in plasma with multiple dosing. As with many drug products for oral inhalation, it is likely that the majority of the inhaled notrealatol delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

In vitro, 61-64% of notrealatol was bound to human plasma proteins at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin was 31%-38% over a range of 5 to 500 ng/mL. The concentrations of notrealatol used to assess plasma protein binding were significantly higher than those achieved in plasma following inhalation of the recommended dose.

Metabolism

Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are known to be involved in the metabolism of notrealatol. However, notrealatol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. It is not known whether patients deficient in CYP 2D6 or 2C19 are at greater risk for systemic adverse effects.

Excretion

In healthy volunteers administered a single oral dose of notrealatol, 59%-62% of the dose was eliminated in the urine and 32%-34% in the feces over a period of 104 hours. The mean elimination half-life was determined to be 10 hours.

In asthma patients, 25-28% of an inhaled dose of notrealatol was excreted in the urine. In COPD patients, 13-16% of an inhaled dose was excreted in the urine.

Gender

After correction for body weight, notrealatol pharmacokinetics did not differ significantly between males and females.

Geriatric, Pediatric, Hepatic/Renal Impairment: The pharmacokinetics of notrealatol have not been studied in the elderly, in children, or in subjects with hepatic or renal impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of notrealatol has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 450 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately 45 times human exposure at the maximum recommended daily inhalation dose). This finding was not observed in the drinking water study, nor was it seen in mice.

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 590 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately 60 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately 25 times human exposure at the maximum recommended daily inhalation dose). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Notrealatol was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis).

13.2 Animal Pharmacology

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

14 CLINICAL STUDIES

14.1 Adolescent and Adult Asthma Trials

In a placebo-controlled, single-dose clinical trial, the onset of bronchodilation (defined as a 15% or greater increase from baseline in FEV_1) was similar for Pretend Inhalizer and albuterol 180 mcg by metered-dose inhaler.

In single-dose and multiple-dose clinical trials, the maximum improvement in FEV_1 for Pretend Inhalizer 15 mcg generally occurred within 1 to 3 hours, and an increase in FEV_1 above baseline was observed for 12 hours in most patients.

Pretend Inhalizer twice daily was compared to albuterol 180 mcg four times daily by metered-dose inhaler, and placebo in a total of 1095 adult and adolescent patients 12 years of age and above with mild-to-moderate asthma (defined as FEV_1 40%-80% of the patient's predicted normal value) who participated in two, 12-week, multi-center, randomized, double-blind, parallel group studies.

The results of both studies showed that Pretend Inhalizer 15 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV_1 for 12 hours post-dose) than placebo throughout the 12-week treatment period. Mean FEV_1 measurements from both studies are shown below for the first and last treatment days. [INSERT FIGURES]

Compared with placebo, patients treated with Pretend Inhalizer 15 mcg demonstrated fewer nighttime awakenings, fewer nights in which patients used rescue medication, and higher morning and evening peak flow rates.

14.2 Pediatric Asthma Trial

A 12-month, multi-center, randomized, double-blind, parallel-group, study compared Pretend Inhalizer and placebo in a total of 520 children with asthma (ages 5-12 years) who required daily bronchodilators and anti-inflammatory treatment. Efficacy was evaluated on the first day of treatment, at Week 12, and at the end of treatment.

Pretend Inhalizer 15 mcg twice daily demonstrated a greater 12-hour FEV_1 AUC compared to placebo on the first day of treatment, after twelve weeks of treatment, and after one year of treatment.

14.3 Adolescent and Adult EIB Trials

The effect of Pretend Inhalizer on exercise-induced bronchospasm (defined as >20% fall in FEV_1) was examined in two randomized, single-dose, double-blind, crossover studies in a total of 38 patients 13 to 41 years of age with exercise-induced bronchospasm. Exercise challenge testing was conducted 15 minutes, and 4, 8, and 12 hours following administration of a single dose of study drug (Pretend Inhalizer 15 mcg, albuterol 180 mcg by metered-dose inhaler, or placebo) on separate test days. Pretend Inhalizer 15 mcg and albuterol 180 mcg were each superior to placebo for FEV_1 measurements obtained 15 minutes after study drug administration. Pretend Inhalizer 15 mcg maintained superiority over placebo at 4, 8, and 12 hours

after administration. The efficacy of Pretend Inhalizer in the prevention of exercise-induced bronchospasm when dosed on a regular twice daily regimen has not been studied.

14.4 Adult COPD Trials

In multiple-dose clinical trials in patients with COPD, Pretend Inhalizer 15 mcg was shown to provide onset of significant bronchodilation (defined as 15% or greater increase from baseline in FEV_1) within 5 minutes of oral inhalation after the first dose. Bronchodilation was maintained for at least 12 hours.

Pretend Inhalizer was studied in two major efficacy, double-blind, placebo-controlled, randomized, multi-center, parallel-group trials in a total of 1634 adult patients (age range: 34-88 years; mean age: 63 years) with COPD who had a mean FEV_1 that was 46% of predicted. The diagnosis of COPD was based upon a prior clinical diagnosis of COPD, a smoking history (greater than 10 pack-years), age (at least 40 years), and spirometry results (prebronchodilator baseline FEV_1 less than 70% of the predicted value, and at least 0.75 liters, with the FEV_1/VC being less than 88% for men and less than 89% for women). These studies included approximately equal numbers of patients with and without baseline brochodilator reversibility, defined as a 15% or greater increase FEV_1 after inhalation of 200 mcg of albuterol sulfate. A total of 400 patients received Pretend Inhalizer 15 mcg twice daily. Each trial compared Pretend Inhalizer 15 mcg twice daily and Pretend Inhalizer 30 mcg twice daily with placebo and an active control drug. The active control drug was ipratropium bromide in COPD Trial A, and slow-release theophylline in COPD Trial B (the theophylline arm in this study was open-label). The treatment period was 12 weeks in COPD Trial A, and 12 months in COPD Trial B.

The results showed that Pretend Inhalizer 15 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV_1 for 12 hours post-dose; the primary efficacy analysis) compared to placebo when evaluated after 12 weeks of treatment in both trials, and after 12 months of treatment in the 12-month trial (COPD Trial B). Compared to Pretend Inhalizer 15 mcg twice daily, Pretend Inhalizer 30 mcg twice daily did not provide any additional benefit on a variety of endpoints including FEV_1. Pretend Inhalizer 15 mcg twice daily was statistically superior to placebo at all post-dose timepoints tested (from 5 minutes to 12 hours post-dose) throughout the 12-week (COPD Trial A) and 12-month (COPD Trial B) treatment periods.

In both trials, compared with placebo, patients treated with Pretend Inhalizer 15 mcg demonstrated improved morning pre-medication peak expiratory flow rates and took fewer puffs of rescue albuterol.

16 HOW SUPPLIED/STORAGE AND HANDLING

Pretend Inhalizer contains: aluminum blister-packaged 15 mcg Pretend (notrealatol) white gelatin capsules with “P” printed on one end and “N” printed on the opposite end; one Inhalizer Inhaler; and FDA-Approved Patient Labeling.

Unit Dose (blister pack), Box of 15 (strips of 5), **NDC XXXX-XXXX-XX**
Unit Dose (blister pack), Box of 75 (strips of 5), **NDC XXXX-XXXX-XX**

Storage and Handling:
***Prior to dispensing*:** Store in a refrigerator, 2ºC-8ºC (36ºF-46ºF)
***After dispensing to patient*:** Store at 20ºC to 25ºC (68ºF to 77ºF). Protect from heat and moisture.

- Pretend capsules should be used with the Inhalizer Inhaler only. The Inhalizer Inhaler should not be used with any other capsules.
- Capsules should always be stored in the blister and only removed IMMEDIATELY before use.
- Always discard the Pretend capsules and Inhalizer Inhaler by the “Use by” date and always use the new Inhalizer Inhaler provided with each new prescription.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.6)

17.1 Acute Exacerbation or Deterioration of Asthma

Pretend Inhalizer is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, $beta_2$-agonist (the health-care provider should provide the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if Pretend Inhalizer treatment becomes less effective, or if they need more inhalations of a short-acting $beta_2$-agonist than usual.

17.2 Excessive Use of Pretend

Patients should not inhale more than the contents of the prescribed number of capsules at any one time. The daily dosage of Pretend Inhalizer should not exceed one capsule twice daily (30 mcg total daily dose). Patients should be advised not to increase the dose or frequency of Pretend Inhalizer without consulting the prescribing physician.

When Pretend Inhalizer is used for the prevention of EIB, the contents of one capsule should be inhaled at least 15 minutes prior to exercise. Additional doses of Pretend Inhalizer should not be used for 12 hours. Prevention of EIB has not been studied in patients who are receiving chronic Pretend Inhalizer administration twice daily and these patients should not use additional Pretend Inhalizer for prevention of EIB.

17.3 Concomitant Therapy

Pretend Inhalizer should not be used as a substitute for oral or inhaled corticosteroids. Patients should be warned not to stop or reduce concomitant asthma therapy without medical advice. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with Pretend Inhalizer.

17.4 Common Adverse Reactions with $Beta_2$-agonists

Patients should be informed that treatment with $beta_2$-agonists may lead to adverse reactions which include palpitations, chest pain, rapid heart rate, tremor or nervousness.

17.5 Instructions for Administering Pretend

Patients should be informed never to use Pretend Inhalizer with a spacer and never to exhale into the device. Patients should avoid exposing the Pretend capsules to moisture and should handle the capsules with dry hands. The Inhalizer Inhaler should never be washed and should be kept dry. The patient should always use the new Inhalizer Inhaler that comes with each refill.

17.6 FDA-Approved Patient Labeling

[Print full text of FDA-approved patient labeling here].