

Overview of Direct-to-Consumer Promotion of Rx Drugs



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FDA-DDMAC

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Functions of DDMAC



⌘ Ensure compliance with FFD&C Act

☑ Not false

☑ Not misleading

☑ Balance between risks and benefits

⌘ Voluntary Compliance

⌘ Enforcement Action

Voluntary Compliance



- ⌘ Guidance documents
- ⌘ Comments when requested
- ⌘ Clarifications of issues and questions

“Promotional” Labeling



⌘ Brochures, booklets, mailing pieces, file cards, bulletins, calendars, price lists, catalogs, letters, videos, slides, exhibits, and similar pieces of printed, audio, or visual matter descriptive of a prescription drug

Advertising



⌘ Advertising -- published journals, magazines, and other periodicals, newspapers, broadcast through media such as television, radio, and telephone communications

FDA Jurisdiction



- ⌘ No laws/regulations prohibit DTC promotion in general or for specific prescription drug products or product classes
- ⌘ Regulatory focus is on the content of the materials **NOT** their general existence

Basics for Promotion



- ⌘ May recommend and suggest the drug ONLY for those uses contained in the approved product labeling
- ⌘ May not be false, lacking in “balance,” or otherwise misleading
- ⌘ Prescription drugs are unique -- the law requires disclosures of the consequences of using the drug

What's False or Misleading

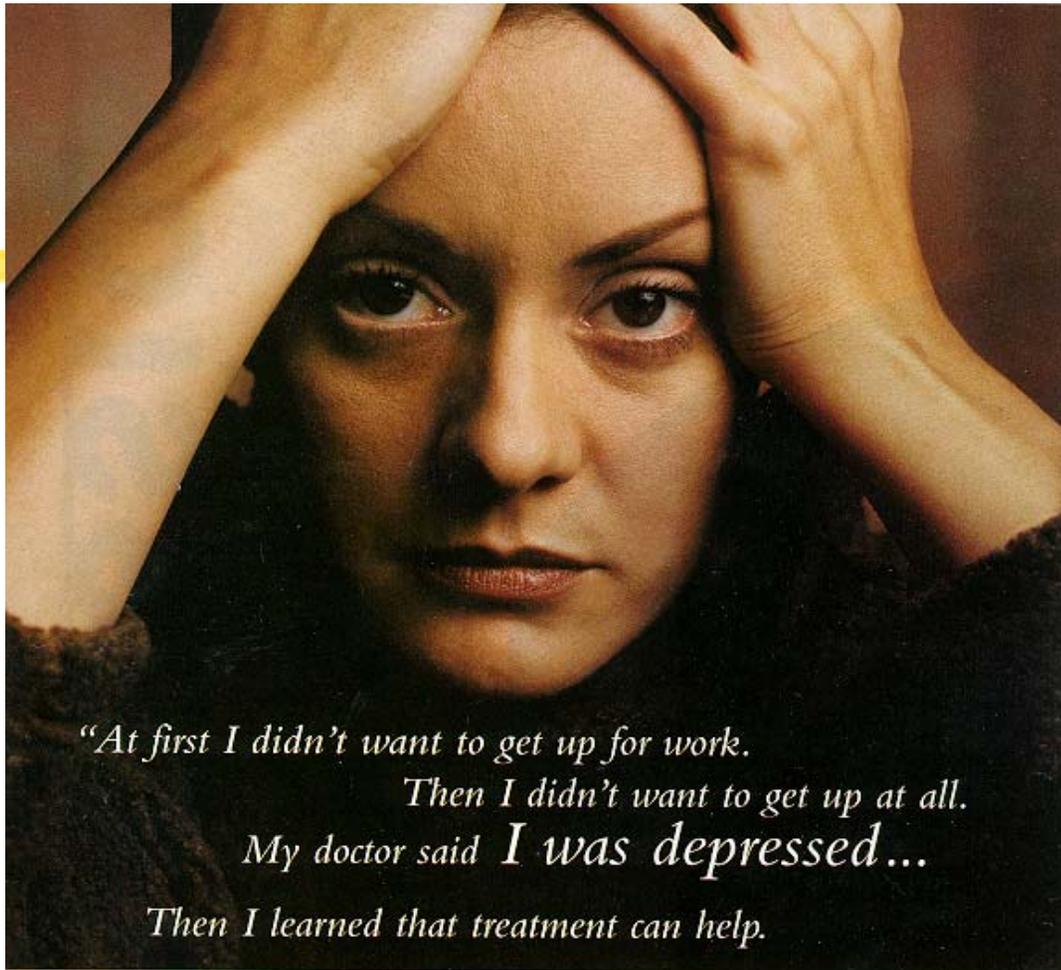


- ⌘ Better or more effective than indicated
- ⌘ Useful in a broader than indicated range of conditions/patients
- ⌘ Safer (fewer side effects, lower severity, incidence)
- ⌘ Comparative claims (better/safer than other products) w/o substantial evidence
- ⌘ Misleading presentation of data, risk relative to benefit, etc.

Types of Promotion



⌘ Help seeking (“see your doctor,” disease oriented) -- these are NOT drug ads



*“At first I didn’t want to get up for work.
Then I didn’t want to get up at all.
My doctor said I was depressed...
Then I learned that treatment can help.*



Now, I’m feeling better.”

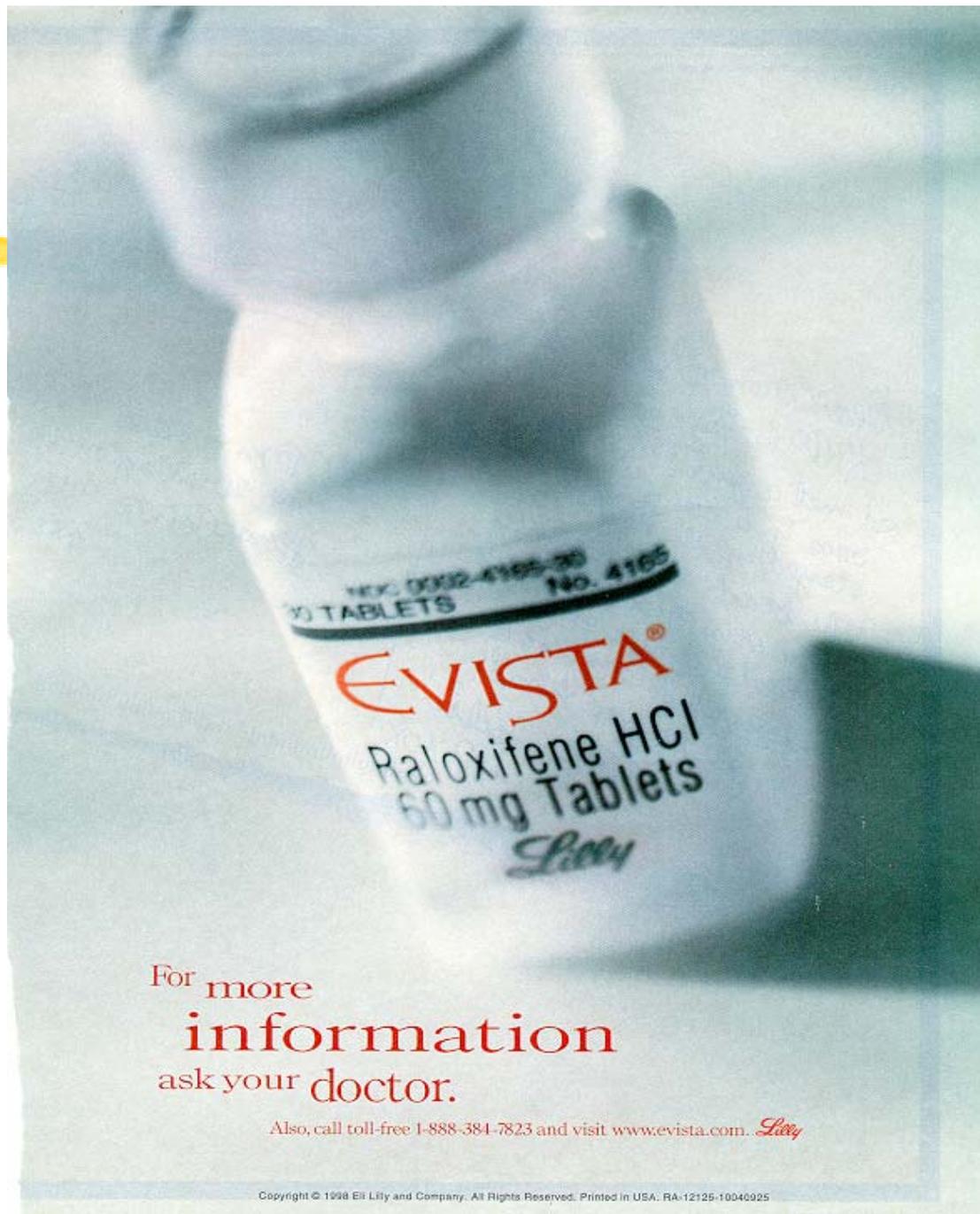
About 1 in 6 Americans will experience depression in their lifetimes. Depression is a condition that can affect people’s jobs, families, and lives. But there is hope. Treatment is available—psychological therapy and antidepressant medicines are among the options that can help relieve depression. In fact, it has been shown that most people who receive treatment improve. Through patient education and research and development of drug therapies, Pfizer is helping millions of people realize that depression can be overcome.

If you’d like to learn more about depression, please call your doctor. For free, confidential brochures about depression, its symptoms, and its treatment, please call: 1-888-549-9422. www.depression-info.com

Life is our life’s work 

Types of Promotion

- ⌘ Reminder -- regulations specifically exempt from disclosure requirements; includes name of product, but no representations beyond dosage form and packaging, price information
 - ☑ not for products with especially serious ("boxed") warnings



For more
information
ask your doctor.

Also, call toll-free 1-888-384-7823 and visit www.evista.com. *Lilly*

Types of Promotion

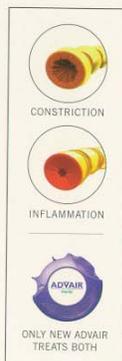
⌘ Product claim

- ☑ claims or representations trigger requirements for accuracy and balance
- ☑ risk disclosure requirement

Do asthma symptoms interfere with your life? You're doing something you enjoy. Then you find yourself wheezing and needing to use your fast-acting inhaler. If this happens more than two times a week, according to the National Institutes of Health, that's a sign that your asthma may be poorly controlled. The good news is, you may be able to do a lot better.

In a 12-week clinical study, new ADVAIR reduced the need for a fast-acting inhaler by an average of 61%.¹ These people needed about 3 puffs per day of their fast-acting inhaler at the start of the study period. They were able to reduce their need for their fast-acting inhaler by an average of 61% by the end of the study. They also experienced more symptom-free days and greater improvement in lung function. (These results were experienced by people taking ADVAIR 100/50, compared with people taking either fluticasone propionate 100 mcg or salmeterol 50 mcg inhalation powders alone.)

How does ADVAIR treat asthma? ADVAIR is the first and only product approved by the FDA to effectively treat the two main components of asthma—constriction (tightening of the muscles surrounding the airways) and inflammation (swelling and irritation of the airways). Please note that ADVAIR does not replace fast-acting inhalers for sudden symptoms.



Please consult accompanying complete Prescribing Information for ADVAIR DISKUS to obtain important information.



Advair is:

*Clinically proven to
reduce the need for
a fast-acting inhaler.*

PRODUCT INFORMATION

ADVAIR™ DISKUS® 100/50
(fluticasone propionate 100 mcg and salmeterol*
50 mcg inhalation powder)

ADVAIR™ DISKUS® 250/50
(fluticasone propionate 250 mcg and salmeterol*
50 mcg inhalation powder)

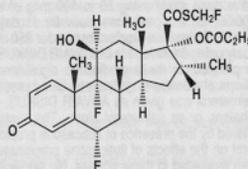
ADVAIR™ DISKUS® 500/50
(fluticasone propionate 500 mcg and salmeterol*
50 mcg inhalation powder)

*As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg

FOR ORAL INHALATION ONLY

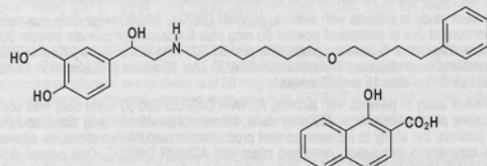
DESCRIPTION: ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is C₂₅H₃₁F₂O₅S. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR DISKUS is salmeterol xinafoate, a highly selective beta₂-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- α -1-[[[6-(4-phenyl)butoxy]hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the empirical formula is C₂₅H₃₇NO₃•C₁₁H₉O₃. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone propionate and

72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose. Each blister contains 1 complete dose of both medications. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 80 L/min for 2 seconds. In adult patients (n = 9) with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV₁] 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS® device was 80.0 L/min (range, 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (n = 13, aged 12 to 17 years) and adult (n = 17, aged 18 to 50 years) patients with asthma inhaling maximally through the DISKUS® device show mean PIF of 122.2 L/min (range, 81.6 to 152.1 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

CLINICAL PHARMACOLOGY:

Mechanism of Action: ADVAIR DISKUS: ADVAIR DISKUS is designed to produce a greater improvement in pulmonary function and symptom control than either fluticasone propionate or salmeterol used alone at their recommended dosages. Since ADVAIR DISKUS contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of medications (a synthetic corticosteroid and a long-acting beta-adrenergic receptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

Fluticasone Propionate: Fluticasone propionate is a synthetic, trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

The precise mechanisms of fluticasone propionate action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol Xinafoate: Salmeterol is a long-acting beta-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₂-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

Pharmacokinetics: ADVAIR DISKUS: Following administration of ADVAIR DISKUS to healthy subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours and those of salmeterol were achieved in about 5 minutes.

In a single-dose crossover study, a higher than recommended dose of ADVAIR DISKUS was administered to 14 healthy subjects. Two inhalations of the following treatments were administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively, and of salmeterol averaged 200 and 150 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate and salmeterol.

In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was administered to 45 asthmatic patients. One inhalation twice daily of the following treatments was administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg alone. Mean peak steady-state plasma concentrations of fluticasone propionate averaged 57, 73, and 70 pg/mL, respectively, indicating

“Brief Summary”



- ⌘ Regulations require that the “brief summary” include “each specific side effect and contraindication” (i.e., all risk concepts)
- ⌘ Manufacturers historically complied by reprinting risk-related sections of product labeling
- ⌘ Verbatim reprinting is not required

“Brief Summary” Broadcast v. Print



- ⌘ Broadcast: media limitations implicitly acknowledged through provision of alternative means of disseminating additional information
- ⌘ Print: little or no leeway to reduce required information

Broadcast Ad Requirements



- ⌘ **Must** have information about “major side effects and contraindications”
 - * in audio or audio plus visual
- ⌘ Can have either:
 - * presentation of a “brief summary,” *or*
 - * “adequate provision” for disseminating product labeling

DTC-Broadcast Guidance



⌘ One possible mechanism for “adequate provision”

Draft guidance issued 8/97

Final guidance issued 8/99

Suggested Information Sources

- ⌘ Toll-free phone -- Package insert ("PI") by mail, [*fax -- in draft guidance only*], read
- ⌘ Reference to a running print advertisement
- ⌘ Healthcare providers -- more info
- ⌘ Internet web page [URL address]

Broadcast Guidance (II)



- ⌘ Multifaceted approach to reach a diverse population
- ⌘ Recognition of diversity of consumer audience
 - * advanced technology access/comfort
 - * active v. passive information seekers
 - * desire to remain anonymous

Basic Communication Requirements



- ⌘ Accurate communication of product indication(s) including context for any claim
- ⌘ Communication of most important risks in a manner reasonably comparable to benefits (presentation and language)
- ⌘ Can't omit important information

Most Important Risks



- ⌘ Specific risk disclosure requirement for broadcast ads -- likely to include:
 - * contraindications (relevant to patients)
 - * major warnings, especially if boxed or bolded
 - * significant precautions/drug interactions
 - * frequent side effects

Considerations



- ⌘ Reasonably comparable communication of risks
- ⌘ Consumer-friendly language for both benefits and risks (readable supers)
- ⌘ Prominence of presentation
- ⌘ Needed context for claims/risks
- ⌘ Information needed for an informed patient-physician discussion

Enforcement Options



- ⌘ Untitled Letters
- ⌘ Warning Letters
- ⌘ Consent Decrees
- ⌘ Penalties
- ⌘ Seizure