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Drug approval and promotion in the **UNITED STATES**

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IMPORTANT **INFORMATION**

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- The slides will progress s at their own pace.
- Do not attempt to speed up the video.
- The Post Test will only unlock after the entire video has been viewed.
- The video can be paused and resumed later.

PROGRAM OBJECTIVES

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After you finish the program, you will be able to:

- List characteristics of Phase 1, Phase 2, Phase 3 and Phase 4 drug trials.
- Identify several historically significant legislation affecting drug regulation.
- Discuss several patent-extension strategies.
- Differentiate between novel and me-too drugs.
- Identify several factors that make a pharmaceutical advertisement misleading.

WHAT IS THE **FOOD AND DRUG ADMINISTRATION (FDA)?**

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- A federal agency established in 1906.
- Part of the Public Health Service (PHS), which is part of the U.S. Department of Health and Human Services (HHS).
- Separate centers within the FDA regulate drugs, biologics, devices, veterinary drugs, food and tobacco.

THE FDA CENTER FOR
DRUG EVALUATION AND RESEARCH (CDER)

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- Approves drugs based on safety and effectiveness.
- Determines over-the-counter vs. prescription status.
- Monitors possible medication side effects through voluntary adverse event reporting.

THE FDA'S **RESPONSIBILITIES**

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The FDA **does not:**

- Regulate the practice of medicine
- Determine optimal therapy for a condition
- Test drugs—it relies on data submitted by the drug sponsor
- Refuse approval for a drug just because there are similar drugs on the market
- Make approval decisions based on the economic impact of a drug for patients or insurers

EFFECTIVE **DRUG REGULATION**

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- In the U.S., safety testing of drugs has only been required since **1938**.
- Evaluation of efficacy has only been required since **1962.**

HISTORY OF DRUG REGULATION IN THE U.S.:
THE EARLY YEARS

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1820

The U.S. Pharmacopeia, the first compendium of standard drugs for the United States, is established.

1848

The Drug Importation Act requires U.S. Customs Service inspection to stop entry of adulterated drugs from overseas.

HISTORY OF DRUG REGULATION IN THE U.S.:
THE EARLY YEARS

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1883

- Dr. Harvey W. Wiley becomes chief chemist, expanding the *Bureau of Chemistry's* studies on food adulteration.
- **Dr. Wiley,** who campaigned for a federal law, is called the ***"Crusading Chemist"*** and ***"Father of the Pure Food and Drugs Act."***

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1902

The Biologics Control Act is passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans.

HISTORY OF DRUG REGULATION IN THE U.S.:
THE EARLY YEARS

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1905

- **"The Great American Fraud"** A series of articles *by Samuel Hopkins Adams,* published in Colliers, exposes the patent medicine industry.
- **The American Medical Association's** Council on Pharmacy and Chemistry initiates a voluntary program of drug approval.

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1906

The original **Food and Drugs Act** is passed by Congress and signed *by President Theodore Roosevelt.* The Food and Drugs Act prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs.

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1911

The Supreme Court rules, in ***U.S. v. Johnson***, that the 1906 Food and Drugs Act does not prohibit false therapeutic claims, but only false and misleading statements about the ingredients or identity of a drug.

HISTORY OF DRUG REGULATION IN THE U.S.:
THE EARLY YEARS

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1937

A tragedy stimulates regulation:

More than 100 people die after taking **Elixir Sulfanilamide,** an antibiotic formulation that contained diethylene glycol. The formula had been tested for flavor but not toxicity.

HISTORY OF DRUG REGULATION IN THE U.S.:
THE EARLY YEARS

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1938

- **The Federal Food, Drug, and Cosmetic (FDC) Act** is passed.
- **The 1938 FDC** act specifies that new drugs must be shown to be safe before marketing.

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THE 1938 FDC ACT'S DEFICIENCIES

- Manufacturers could sell a drug if the FDA didn't act within 60 days to prevent its marketing.
- FDA had no authority to enforce good manufacturing processes.

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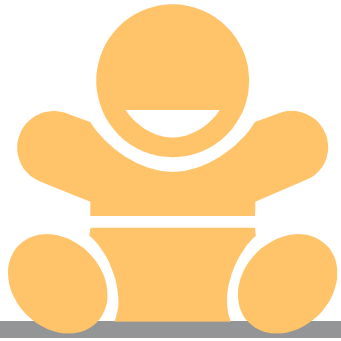
1961

Another tragedy spurs regulation:

- 10,000 thalidomide-exposed infants in Europe are born with deformed limbs.
- Due to efforts of FDA Medical Director Frances Kelsey, thalidomide is not approved in the U.S.



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THALIDOMIDE

- Drug samples of thalidomide are sent to 1200 physicians before the FDA rejects the drug in 1961.
- At least 17 deformed babies are born in the U.S.

HISTORY OF DRUG REGULATION IN THE U.S.:
THE EARLY YEARS

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1962

- President Kennedy signs the **Kefauver-Harris Amendments** to the Food, Drug, and Cosmetics Act into law.
- For the first time, drug manufacturers must prove to the FDA that a product is effective before marketing it.

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The Kefauver-Harris Amendments

- Require manufacturers to report serious side effects
- Require adequate and well-controlled clinical studies conducted by qualified experts
- Require FDA approval before a drug could be marketed
- Allow FDA to set good manufacturing practices for industry
- Give FDA control of prescription drug advertising

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BRINGING
A DRUG TO MARKET

BRINGING A DRUG TO MARKET

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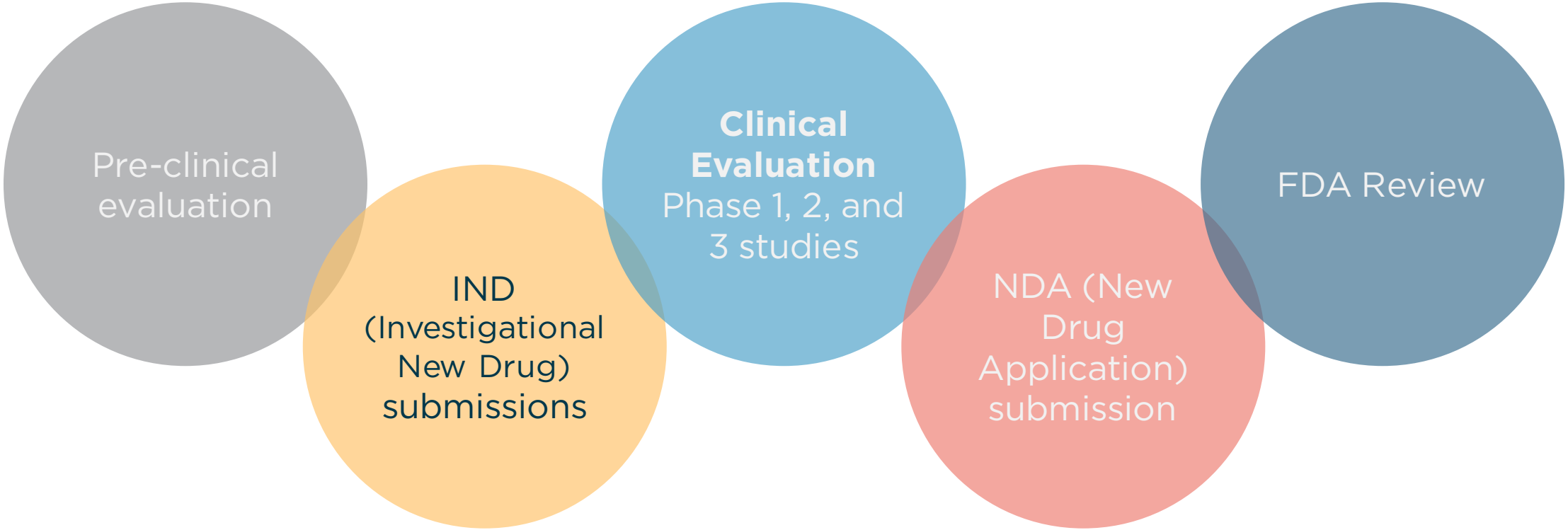
Drug Approval Requires:



DRUG-TO-MARKET **TIMEFRAME**

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It takes approximately 8-9 years to bring a drug to market, from the first experimental animal tests to the final approved product.

PRECLINICAL Studies

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Computer simulations, experimental animal studies, or in vitro studies are performed to:

- Identify a promising drug
- Test for promising biologic effects
- Test for adverse effects

PRECLINICAL Responsibilities

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- A drug company may test many related compounds to identify one or two to take further in development.
- The FDA is not involved in this aspect of drug development, but will review the study results for any compounds that are planned for clinical (human) testing.

THE INVESTIGATIONAL **NEW DRUG APPLICATION** *(IND)*

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The IND is the formal process by which a sponsor requests approval for testing of a drug in humans. It includes:

- Information developed during preclinical testing regarding safety and effectiveness.
- An "investigator brochure" that ensures that institutional review boards (IRBs) are adequately informed about possible effects of the drug.

Clinical studies can begin after the FDA approves an IND.

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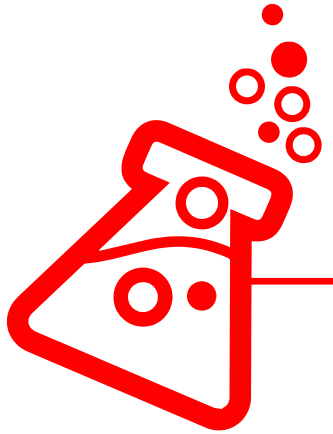
CLINICAL TESTING



Phase #1

PHASE 1 STUDIES ARE USUALLY CONDUCTED IN HEALTHY VOLUNTEERS, AND ARE NOT CONTROLLED.

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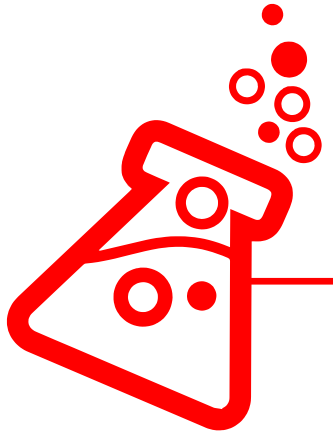
The goal of a Phase 1 study is:

- To determine what the drug's most frequent side effects are.
- Often, to determine how the drug is absorbed, distributed, broken down, and excreted.

The number of subjects in Phase 1 studies ranges from 20 to about 80.



Phase #2

PHASE 2 STUDIES BEGIN IF THE DRUG'S TOXICITY IS ACCEPTABLE IN PHASE 1.

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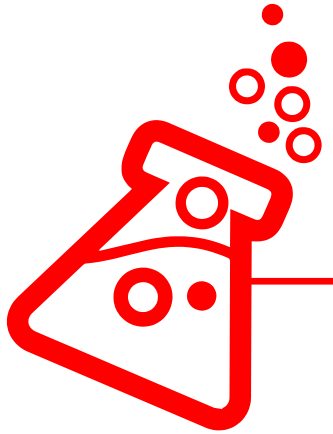
The goal of a Phase 2 study is:

- To obtain preliminary data on whether the drug works in people who have a specific disease or condition.
- For controlled trials, patients receiving the drug are compared with similar patients receiving a placebo or a different drug.
- Safety continues to be evaluated.

The number of subjects in Phase 2 studies ranges from a few dozen to about 300.

After Phase #2

At the end of Phase 2, the FDA and sponsors negotiate how the large-scale studies in Phase 3 should be done.



Phase #3

PHASE 3 STUDIES BEGIN IF EVIDENCE OF EFFECTIVENESS IS SHOWN IN PHASE 2

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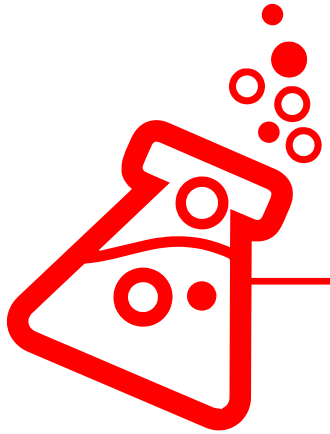
Phase 3 studies:

- Are usually placebo-controlled
- Gather more information about safety and effectiveness
- May test different dosages
- May test the drug in different populations
- Are often multi-center trials

Usually, Phase 3 studies include several hundred to about 3000 subjects.



Phase #3

STUDIES ARE CONTROLLED

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- Controlled clinical trials compare the new drug to a placebo or to an existing therapy.
- The standard for effectiveness may be statistical superiority to the placebo or “non-inferiority” to an existing therapy.

NDA Submission

- Submission of an NDA is the formal step the sponsor takes to have FDA consider a drug for marketing approval.
- The NDA, which can be hundreds of thousands of pages, includes the results of preclinical and clinical study results, manufacturing information, and labeling.

After an **NDA** IS RECEIVED

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- The FDA has 60 days to decide whether to file (accept) it so it can be reviewed.
- If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
- After deciding that it will review an NDA, the FDA has 10 months to make a determination (6 months for priority drugs).

FDA *Review*

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- The **FDA** reviews information that goes on both the drug's professional and patient labeling.
- The **FDA** inspects the facilities where the drug will be manufactured as part of the approval process.
- Evaluation of manufacturing is part of the **NDA** process.
    - The sponsor must show that the product entering to market is the same as the product tested in trials.

NDA *decisions*

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Drug Approval Requires:

Approved

The drug can be marketed.

Approvable

Some issues need to be resolved prior to approval.

Not approvable

Indicates significant deficiencies--it is unclear that approval can be obtained in the future, at least without substantial additional data.

The PRODUCT LABEL

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- The product label is written and owned by the manufacturer, but approved by the FDA.
- Categories of information that are required in the label are set forth in the Code of Federal Regulations.
- Exact label language is often negotiated between the sponsor and the FDA.
- Once approved by the FDA, the label governs the information that can be distributed by the sponsor, including materials distributed by industry representatives.

POST-MARKETING *(Phase 4)* studies

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Phase 4 trials are any trials that are done after the drug is on the market.

- Usually, Phase 4 trials are not required, but sometimes the FDA may require the sponsor to do additional Phase 4 studies after marketing to examine a safety concern.
- A manufacturer may do a Phase 4 trial of a drug in a population or for a condition that wasn't assessed prior to approval.

“ON-LABEL” *and* “OFF-LABEL”

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- All information distributed by drug manufacturers must be “on-label” – consistent with the drug label.
- It is illegal for pharmaceutical companies to promote a drug “off-label” – conditions for which the FDA has not determined that the benefits outweigh the risks.
- Prescribers are allowed to prescribe a drug “off-label.”

Who pays for DRUG EVALUATION?

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- The FDA is mostly funded by Congress, but about half the budget for drug evaluations is paid by the pharmaceutical industry.
- The **Prescription Drug User Fee Act (PDUFA)**, passed in 1992, provides funding of FDA regulatory activities by those being regulated. PDUFA also limits the time within which the FDA must complete its review of an NDA.

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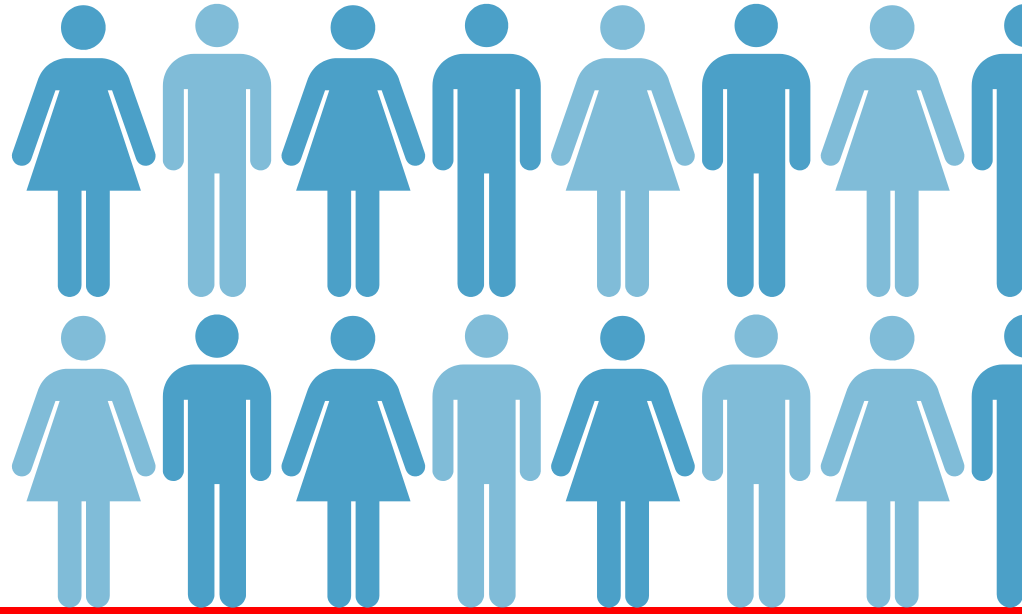
STUDYING A **DRUG ON THE MARKET**

Post-Marketing Surveillance



Advantages of POST-MARKETING SURVEILLANCE

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Adverse events are assessed before marketing, but premarketing studies can't pick up all adverse events. Why?

- Study populations are relatively small, so only the most common adverse events may be discovered.
- Short-term trials can't pick up long-term events.
- Clinical trial populations are usually healthier than real-world populations.

Food and Drug Administration MEDWATCH

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- Medwatch is the FDA's safety information and adverse event reporting program for drugs, devices, biologics, and dietary supplements.
- The U.S. has a voluntary adverse event reporting system; healthcare providers are encouraged, but not required, to report adverse events.
- **Although adverse event reporting is voluntary for healthcare providers, it is mandatory for drug manufacturers.**

- The FDA monitors adverse event reports, and looks for signals (groups of similar events).
- Less than 1% of adverse events are reported, which hampers early detection of problems.
- Anyone can report adverse events related to an FDA-regulated product.

Food and Drug Administration MedWatch

REPORTING IS **EASY**

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- An adverse event should be reported even if you are not sure it is related to a therapy.
- Reports can be made online, or on paper. The FDA provides prepaid postage for paper forms.

www.FDA.gov/Safety/MedWatch

RISK EVALUATION *and* MITIGATION STRATEGY (REMS)

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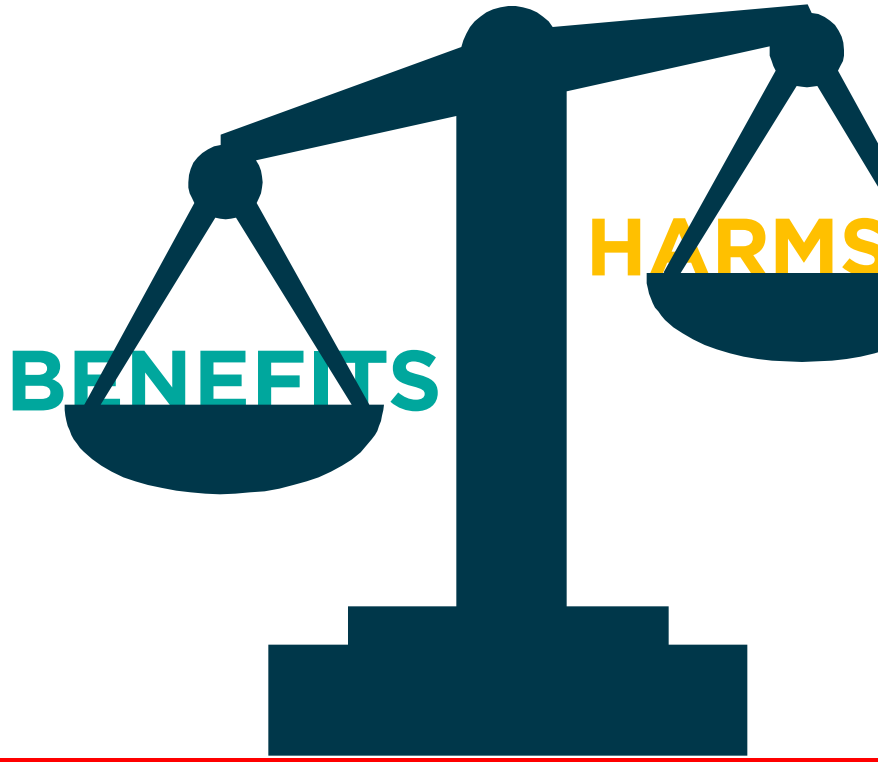
- The FDA Amendments Act of 2007 gave the FDA authority to require a Risk Evaluation and Mitigation Strategy (REMS), which are management plans to ensure that the benefits of certain prescription drugs outweigh their risks.
- FDA can require a REMS before or after a drug is approved.
- Drug sponsors develop REMS programs, and the FDA reviews and approves them.



REMS: *examples*

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- Use of a drug that can cause liver failure may require liver function test monitoring.
- Use of a drug that can cause a serious allergic reaction may require that providers are certified before they can prescribe it.
- Use of a drug that can cause birth defects may require a negative pregnancy test before using it.

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PHARMACEUTICAL ADVERTISING *and* PROMOTION

Regulating Promotion

Ads are not PRE-APPROVED

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The FDA does not pre-approve advertisements or other promotional material, but drug companies must send all ads and promotional material to the FDA.

PRE-LAUNCH *promotion*

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- Promotion of a drug starts years before regulatory approval is expected.
- Companies cannot legally promote a drug "pre-launch" before approval, but indirect marketing is allowed.
- More money is spent on promoting a drug in the three years prior to launch than in the first year after the drug arrives on the market.

Pre-launch: "COMING SOON"

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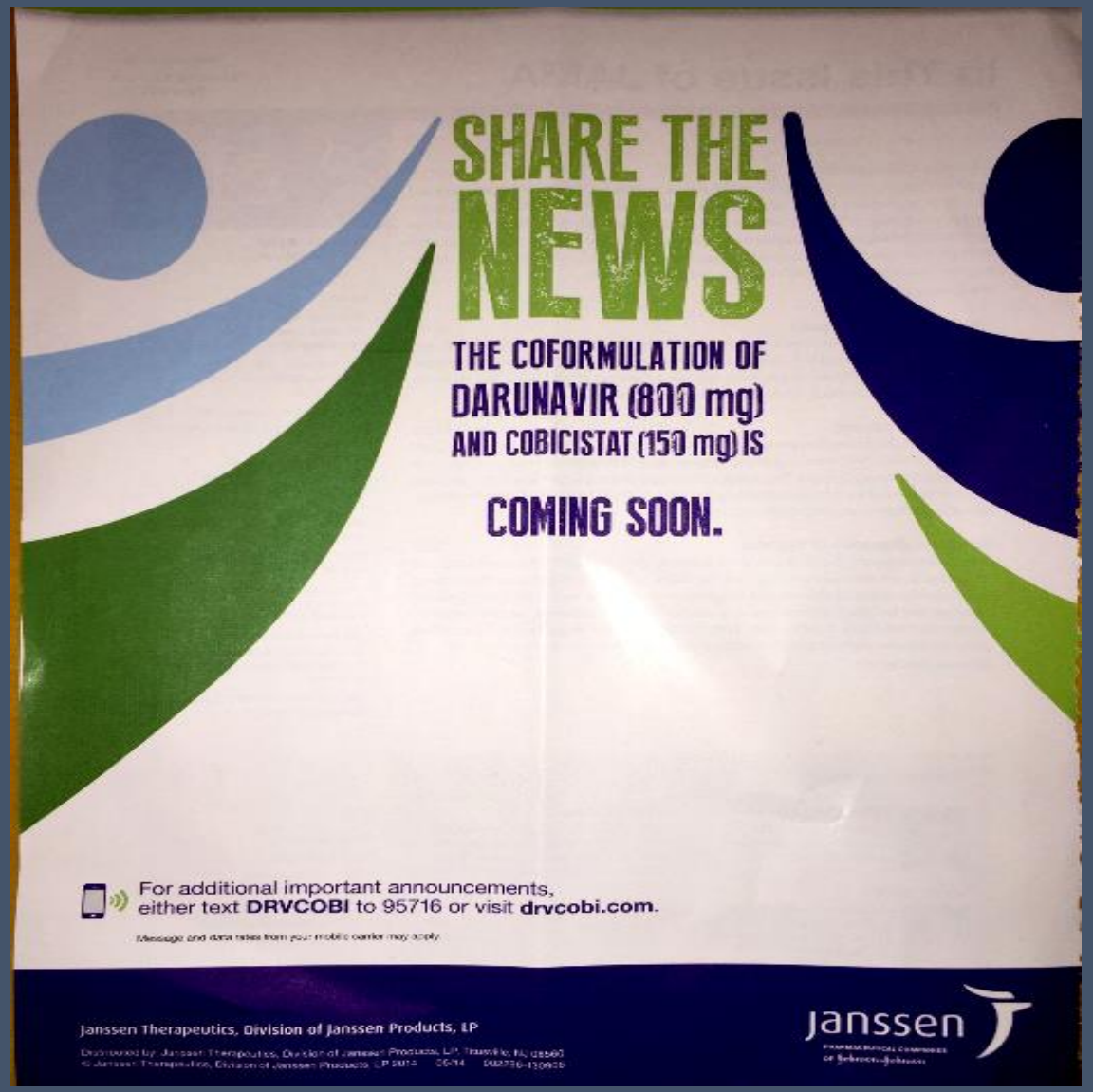
Pre-launch Ads:

- Pique interest in a new product
- Introduce logos and color schemes
- Introduce the brand name


Coming soon
Januvia™
(sitagliptin phosphate)
Sign up at Januvia.com to receive more information as it becomes available.
MERCK


Coming soon
A new development in the treatment of hypertension
www.newforestdrug.com
Forest Laboratories, Inc.


SHARE THE NEWS
THE COFORMULATION OF DARUNAVIR (800 mg) AND COBICISTAT (150 mg) IS
COMING SOON.
For additional important announcements, either text DRVCOBI to 95716 or visit drvcobi.com.
Janssen Therapeutics, Division of Janssen Products, LP
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EXPRESS
Coming Soon.
URGENT
Very Soon.
RUSH
Patanase
(olopatadine HCl) 665 mcg
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Indirect marketing: PROMOTION WITHOUT MENTIONING THE PRODUCT

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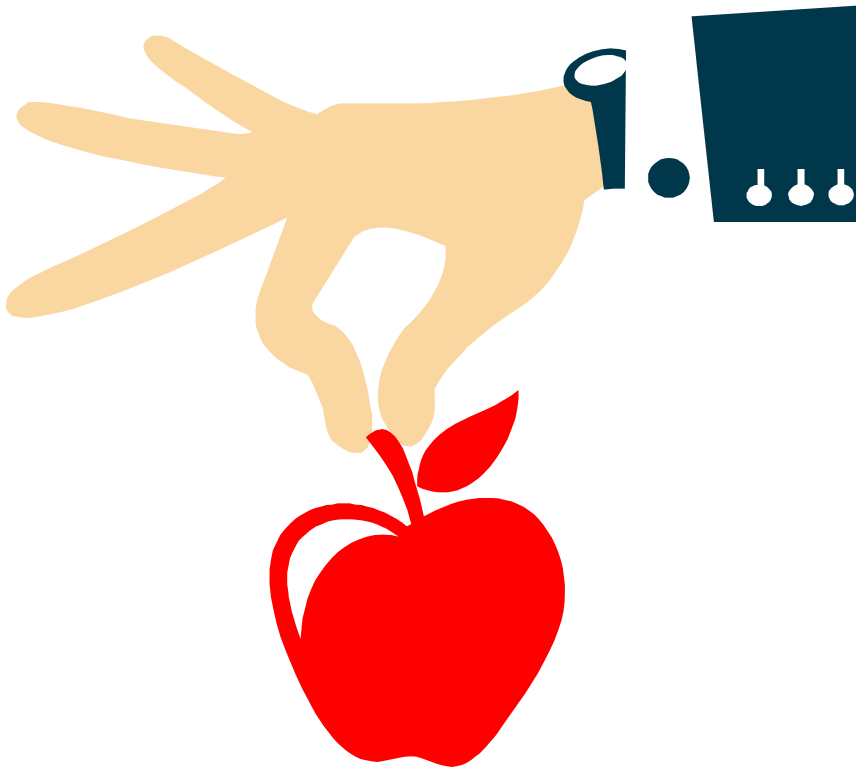
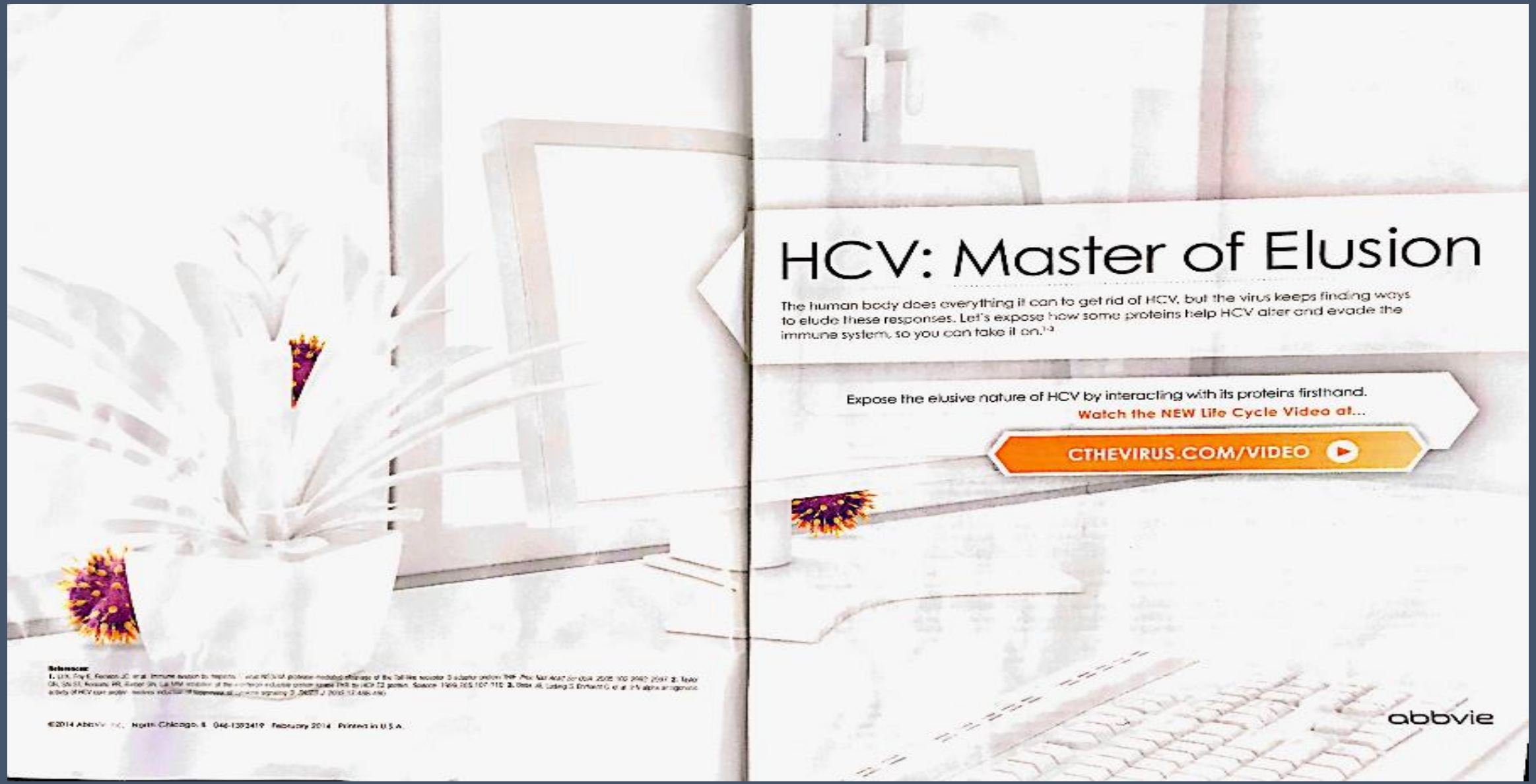
Indirect marketing includes:

- "Disease awareness" (also called "Disease Mongering")
  - Promoting a condition that a targeted therapy treats
- Mitigating negative perceptions of a product
- Disparaging competing products





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RETHINK HCV

HCV CAN BE CURED

ADVANCES IN HCV MANAGEMENT HAVE MADE CURE MORE POSSIBLE FOR PATIENTS.

More than 75% of patients with HCV are baby boomers, persons born between 1945 and 1965.[1]
The CDC, USPSTF, and AASLD now recommend the one-time screening of all baby boomers, regardless of risk factors.[8-10]

Additionally, scientific advances have made HCV treatment shorter and more effective.

Cure, also known as sustained virologic response (SVR), is defined as undetectable HCV in the blood at 12 or more weeks after therapy is complete.[8,11]

Take action now: Screen. Diagnose. Refer.
Request the HCV Toolkit at HCVcanbecured.com/kit4

By 2007, the **HCV mortality rate surpassed that of HIV,** and continued to rise.[4-6]

Of the approximately **3.5 million Americans** with chronic hepatitis C virus (HCV) infection, half have been diagnosed, and about **9% have been successfully treated.**[1]

In the US, HCV is now the leading cause of **liver transplantation**[2] **and liver cancer.**[3]

References: 1. Yoon SR et al. PLoS ONE. 2013;8(7):1-7. 2. Kim WR et al. Am J Transplant. 2014;14(suppl 1):69-78. 3. El-Serag HB. Gastroenterology. 2012;142(6):1264-1273.e1. 4. Ly KN et al. Ann Intern Med. 2012;156(4):271-278. 5. Murphy SL et al. http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf. Accessed October 29, 2014. 6. CDC. http://www.cdc.gov/hepatitis/statistics/2014surveillance. Accessed October 29, 2014. 7. CDC. http://www.cdc.gov/hepatitis/HCV/index.htm. Accessed October 29, 2014. 8. Smith BD et al. MMWR Recomm Rep. 2012;61(RR-4):1-32. 9. USPSTF. http://www.uspreventiveservicestaskforce.org/uspstf12/hepc/hepcfinalrs.htm. Accessed October 29, 2014. 10. AASLD, IDSA, IAS-USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed September 16, 2014. 11. US Department of Health and Human Services, Center for Drug Evaluation and Research. Draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013.


Cholesterol never sleeps.
A substantial number of patients at the highest risk receiving therapy are unable to achieve LDL-C goal.
~70% of patients at the highest risk who are receiving therapy do not achieve an optional LDL-C goal of <70 mg/dL (1.8 mmol/L).1*
Are your patients at risk? Learn more at www.CholesterolNeverSleeps.com
*Data are from a 2006–2007 multinational survey, of which 2,334 patients were considered very high risk (defined as CHD plus two or more risk factors). National Cholesterol Education Program (NCEP) Adult Treatment Panel III U.S. optional goal is <70 mg/dL (1.8 mmol/L). Countries in the survey included the United States, Canada, Spain, the Netherlands, France, Taiwan, Korea, Brazil, and Mexico.
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Launch: "NOW AVAILABLE"

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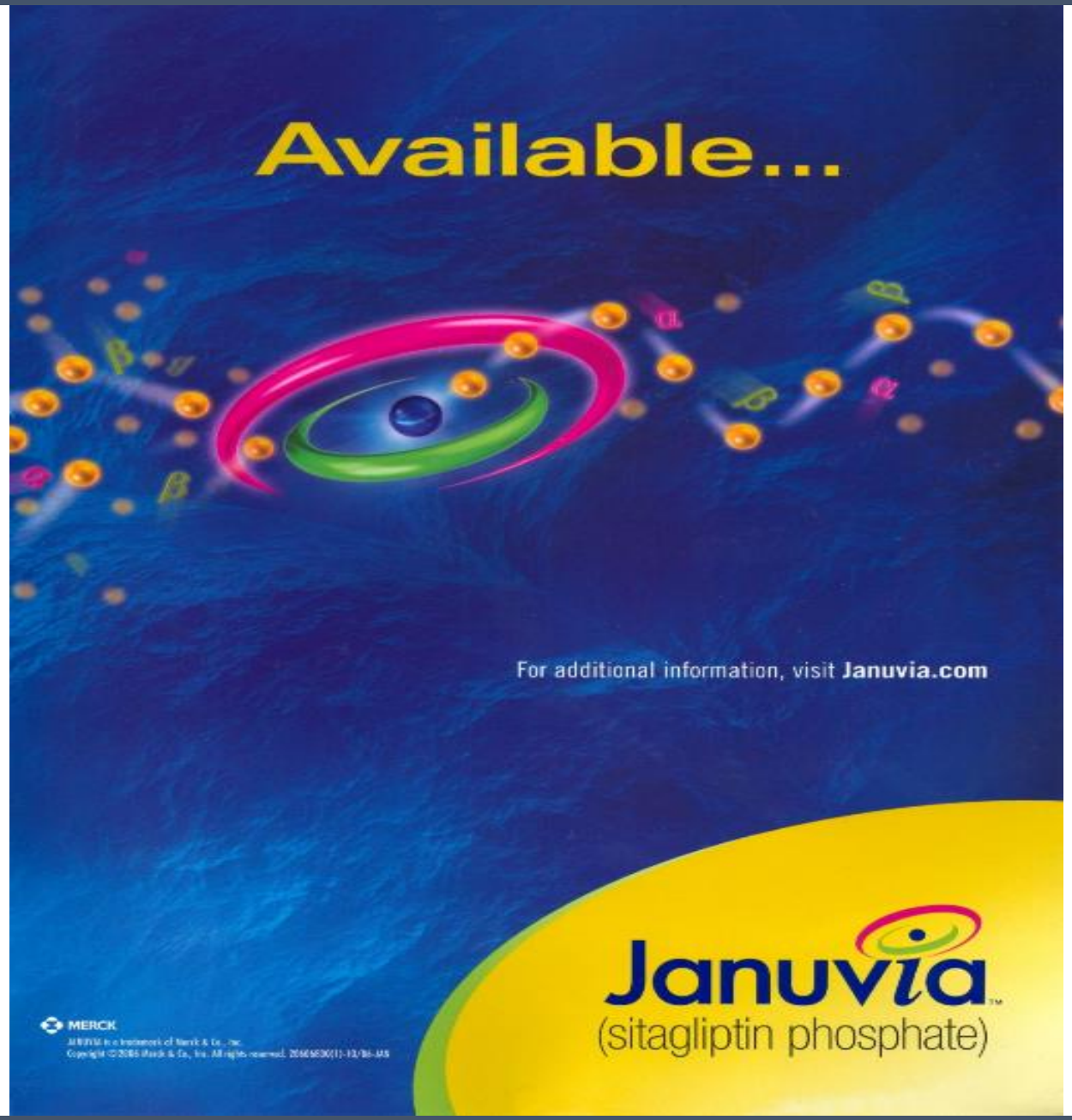
Announcement of the Availability of a New Drug


Available...
For additional information, visit Januvia.com
MERCK
Januvia
(sitagliptin phosphate)


NOW APPROVED
farxiga™
(dapagliflozin) 5mg tablets
Learn more at farxiga-info.com
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FARXIGA™ is a trademark of Bristol-Myers Squibb Company.
01/14
Bristol-Myers Squibb
AstraZeneca


RELISTOR®
methylnaltrexone bromide
subcutaneous injection
NOW APPROVED
FOR THE TREATMENT OF OPIOID-INDUCED CONSTIPATION IN ADULT PATIENTS WITH CHRONIC NON-CANCER PAIN.
In a clinical study of patients with chronic non-cancer pain who suffered from opioid-induced constipation:
6 out of 10 RELISTOR® (methylnaltrexone bromide) patients had at least 3 SBMs* per week[1]
33% of patients taking RELISTOR experienced an SBM* within 4 hours of their first dose[1]
• RELISTOR targets the underlying cause of opioid-induced constipation without affecting analgesia[2]
• RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction[2]
• In the clinical study in adult patients with opioid-induced constipation and chronic non-cancer pain, the most common adverse reactions (≥ 1%) were abdominal pain (21%), nausea (9%), diarrhea (6%), hyperhidrosis (6%), hot flush (3%), tremor (1%), and chills (1%).
*Spontaneous Bowel Movement occurring without the use of rescue laxatives.
Indication
RELISTOR is indicated for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain.
Important Safety Information about RELISTOR
RELISTOR® (methylnaltrexone bromide) Subcutaneous injection is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation.
Cases of gastrointestinal perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using RELISTOR in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain. Discontinue RELISTOR in patients who develop this symptom.
If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician.
Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia and should be monitored for adequacy of analgesia and symptoms of opioid withdrawal.
Avoid concomitant use of RELISTOR with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.
RELISTOR may precipitate opioid withdrawal in a fetus and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In nursing mothers, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
In the clinical study in adult patients with opioid-induced constipation and chronic non-cancer pain, the most common adverse reactions (≥ 1%) were abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor, and chills.
In clinical studies in adult patients with opioid-induced constipation and advanced illness, the most common adverse reactions (≥ 5%) were abdominal pain, flatulence, nausea, dizziness, and diarrhea.
Please see Brief Summary of complete Prescribing Information for RELISTOR on the adjacent page.
References
1. Mehta E, Bonaiy ER, Schulman S, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic nonmalignant pain: a randomized controlled study. J Pain. 2011;12(5):594-602.
2. RELISTOR® (methylnaltrexone bromide) Prescribing Information. Salix Pharmaceuticals, Inc.
Salix

ACTIVE MARKETING

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Promoting
a drug in the market

THE POWER TO HELP THEM QUIT

DUAL ACTION FOR SMOKING CESSATION

- CHANTIX™ (varenicline) has agonist and antagonist effects at $\alpha_4\beta_2$ nicotinic acetylcholine receptors

QUIT RATES SUPERIOR TO ZYBAN® AT 12 WEEKS IN 2 HEAD-TO-HEAD CLINICAL TRIALS (P=.0001)[1,2a]

44% of subjects who received CHANTIX 1 mg bid quit smoking by the end of 12 weeks vs:

- Approximately 30% of subjects who received Zyban 150 mg bid
- Approximately 175% of subjects who received placebo

WELL-STUDIED TOLERABILITY AND SAFETY PROFILE

- The most common adverse reactions included nausea, sleep disturbance, constipation, flatulence, and vomiting. Nausea occurred in 30% of subjects while 3% discontinued due to nausea

CONVENIENT *PAK* DOSING

- *PAK*s are designed to simplify prescribing and to help improve patient adherence

GET QUIT™ SUPPORT PLAN

- A personalized behavioral support program designed to address critical behavioral components of smoking cessation, such as relapse

Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.

Dosage adjustment with CHANTIX is recommended in patients with severe renal impairment or in patients undergoing hemodialysis.

Smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, such as theophylline, warfarin, and insulin. Dosage adjustment for these drugs may be necessary.

CHANTIX is indicated as an aid to smoking cessation treatment in adults.

Safety and efficacy of CHANTIX in combination with other smoking cessation drug therapies have not been studied.

CHANTIX™ (varenicline) TABLETS

TURN MORE SMOKERS INTO QUITTERS

Zyban is a registered trademark of Glaxo Group Limited.

References: 1. Food and Drug Administration, Center for Drug Evaluation and Research. Approval package for: application number NDA 21-928 statistical review(s). Food and Drug Administration Web site. Available at: http://www.fda.gov/cder/foi/nda/2006/021928_s000_Chantix_StatR.pdf. Accessed August 25, 2006. **2.** Data on file. Pfizer Inc. Post hoc analysis of data from nine study reports. **3.** Gonzales D, Rennard SI, Nides M, et al, for the Varenicline Phase 3 Study Group. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:47-55. **4.** Jorenby DE, Hays JT, Rigotti NA, et al, for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:56-63. **5.** CHANTIX [package insert]. New York, NY: Pfizer Inc; May 2007.

www.pfizerpro.com/chantix

Please see brief summary of Prescribing Information on last page of this advertisement.

*Results from 2 identically designed, 52 week (12 weeks pharmacotherapy, 40 weeks nonpharmacotherapy follow-up), randomized, double-blind, parallel-group, multicenter clinical trials (study 4: N=1022; study 5: N=1023) in which CHANTIX 1 mg bid was compared with Zyban 150 mg bid and placebo for efficacy and safety in smoking cessation. For trial inclusion, subjects must have smoked at least 10 cigarettes per day over the past year, with no period of abstinence greater than 3 months, and must have been bupropion naïve. The primary efficacy end point in both trials was the carbon monoxide (CO)–confirmed 4-week continuous abstinence rate for weeks 9 through 12, defined as the percentage of subjects who reported no smoking (not even a puff) or use of any nicotine-containing products confirmed by an exhaled CO measurement of 10 ppm or less at each clinic visit. (Studies 4 and 5 from the CHANTIX package insert.)[1,2a]

Subjects were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each clinic visit in accordance with Agency for Healthcare Research and Quality guidelines.[3]


RELISTOR®
methylnaltrexone bromide
subcutaneous injection
When 1st-line laxative therapy isn't enough for patients with advanced illness,*
OPIOID-INDUCED CONSTIPATION MAY NEED RELISTOR-INDUCED RELIEF.
• Opioid-induced constipation (OIC) is unique and often unresponsive to laxative therapy[1]
• RELISTOR® (methylnaltrexone bromide) targets the underlying cause of OIC without affecting analgesia[2]
• In a single-dose study, most patients experienced a BM within 4 hours of the first dose and ≥3 weekly BMs when dosed every other day in a multi-dose study[2,3]
• The most common adverse reactions in clinical trials with RELISTOR were abdominal pain, flatulence, nausea, dizziness, diarrhea, and hyperhidrosis[2]
For more information, go to RELISTOR.com.
Indication
RELISTOR is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied.
Important Safety Information about RELISTOR
RELISTOR® (methylnaltrexone bromide) Subcutaneous Injection is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.
Cases of gastrointestinal (GI) perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract (i.e., cancer, peptic ulcer, Ogilvie's syndrome). Perforations have involved varying regions of the GI tract (e.g., stomach, duodenum, or colon). Use RELISTOR with caution in patients with known or suspected lesions of the GI tract. Advise patients to discontinue therapy with RELISTOR and promptly notify their physician if they develop severe, persistent, or worsening abdominal symptoms.
If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician.
Use of RELISTOR beyond four months has not been studied.
Safety and efficacy of RELISTOR have not been established in pediatric patients.
The most common adverse reactions reported with RELISTOR compared with placebo in clinical trials were abdominal pain (28.5%), flatulence (13.3%), nausea (11.5%), dizziness (7.3%), diarrhea (5.5%), and hyperhidrosis (6.7%).
*Can include cardiovascular disease, cancer, and COPD.
References
1. Thomas JR, Cooney GA. Palliative care and pain: new strategies for managing opioid bowel dysfunction. J Palliat Med. 2008;11(suppl 1):S1-S10.
2. RELISTOR prescribing information. Raleigh, NC: Salix Pharmaceuticals, Inc.
3. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med. 2008;358(22):2332-2343.
Please see Brief Summary of complete Prescribing Information on the adjacent page.
www.salix.com
8510 Colonnade Center Drive, Raleigh, NC 27615
For additional information, call: 1-888-SLNP (7567)
To report adverse events, call: 1-800-308-0024
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PATENT EXTENSION and EVERGREENING

STRATEGIES for **PATENT EXTENSION**

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Evergreening is an industry strategy for maintaining a market for a drug and variations on that drug. Tactics include:

- Prolonged-action preparations
- Minor changes in dosing
- Fixed-dose combinations
- Enantiomers
- Metabolites, prodrugs, analogs
- Renaming

PROLONGED ACTION PREPARATIONS

- Controlled-release **(CR)**
- Sustained-release **(SR)**
- Extended-release **(XL)**
- Long-acting **(LA)**

Tablets not actual size. Not actual patient.

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

OxyContin® contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit *[see Warnings and Precautions (5.1)]*. Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving OxyContin for signs of misuse, abuse, and addiction during treatment *[see Drug Abuse and Dependence (9)]*.

Life-Threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of OxyContin, even when the drug has been used as recommended and not misused or abused *[see Warnings and Precautions (5.2)]*. Proper dosing and titration are essential and OxyContin should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of OxyContin or following a dose increase. Instruct patients to swallow OxyContin tablets intact. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of oxycodone.

Accidental Exposure

Accidental ingestion of OxyContin, especially in children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.3)]*.

Please see Additional Warnings and Precautions on the following page.
Please read Brief Summary of Full Prescribing Information on the following pages, including Boxed Warning.

Because your patients' pain treatment needs may change over time

Reassess at every step

Every-12-hour OxyContin Tablets

OxyContin 60 mg and 80 mg tablets are for use in opioid-tolerant patients only. Ingestion of these strengths of OxyContin Tablets may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.

Indications and Usage

OxyContin is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Use

OxyContin is not for use:

- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- In the immediate postoperative period (the first 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time

OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

Contraindications

OxyContin is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus and gastrointestinal obstruction
- Hypersensitivity (e.g., anaphylaxis) to oxycodone

For information about or to print OxyContin Savings Cards for your eligible patients, please visit PurdueHCP.com/SavingsProgram

OXYCONTIN® CII
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

Ambien CR (Controlled-Release)

Granting a new patent:
MINOR CHANGES IN DOSING

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Examples:

- **Yasmin**
  *(ethinyl estradiol **30** mcg/ drospirenone 3 mg)*
- **Yaz**
  *(ethinyl estradiol **20** mcg/ drospirenone 3 mg)*
- **Androgel**
  (topical testosterone 1% vs. 1.62%)

"Aricept 23 mg... did not show improvement on overall patient functioning. In the study, more people who took Aricept 23 mg experienced increased side effects."

FIXED-DOSE COMBINATIONS

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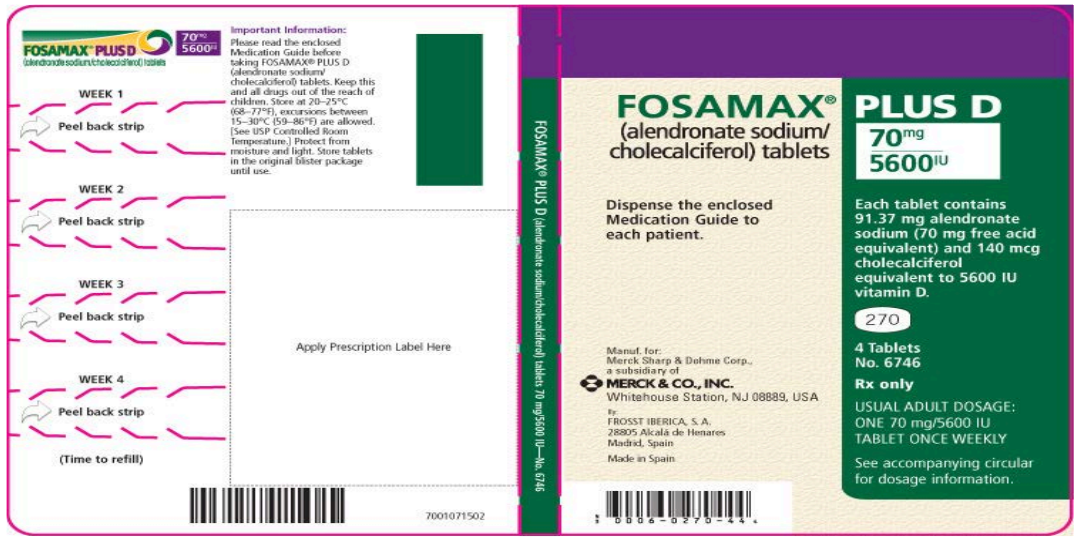
Fixed-dose combinations are two or more drugs in one pill. Even if both drugs are off patent, a new patent can be obtained for the combination.

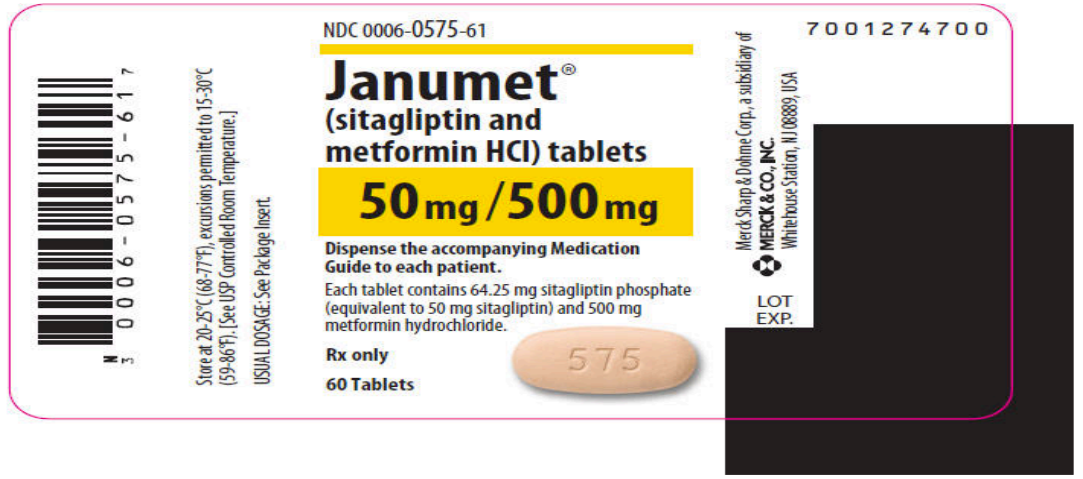
Fixed-dose combinations:

- Are often more expensive than their components.
- Provide less flexibility in dosing options.

Examples


FOSAMAX PLUS D
70mg 5600IU
(alendronate sodium/cholecalciferol) tablets
Important Information:
Please read the enclosed Medication Guide before taking FOSAMAX® PLUS D (alendronate sodium/cholecalciferol) tablets. Keep this and all drugs out of the reach of children. Store at 20–25°C (68–77°F), excursions between 15–30°C (59–86°F) are allowed. [See USP Controlled Room Temperature.] Protect from moisture and light. Store tablets in the original blister package until use.
WEEK 1
Peel back strip
WEEK 2
Peel back strip
WEEK 3
Peel back strip
WEEK 4
Peel back strip
(Time to refill)
Apply Prescription Label Here
7001071502
FOSAMAX® PLUS D (alendronate sodium/cholecalciferol) tablets 70 mg/5600 IU—No. 6746
FOSAMAX®
(alendronate sodium/
cholecalciferol) tablets
Dispense the enclosed Medication Guide to each patient.
Manuf. for:
Merck Sharp & Dohme Corp.,
a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
By:
FROSST IBERICA, S.A.
28805 Alcalá de Henares
Madrid, Spain
Made in Spain
PLUS D
70mg
5600IU
Each tablet contains 91.37 mg alendronate sodium (70 mg free acid equivalent) and 140 mcg cholecalciferol equivalent to 5600 IU vitamin D.
270
4 Tablets
No. 6746
Rx only
USUAL ADULT DOSAGE:
ONE 70 mg/5600 IU
TABLET ONCE WEEKLY
See accompanying circular for dosage information.

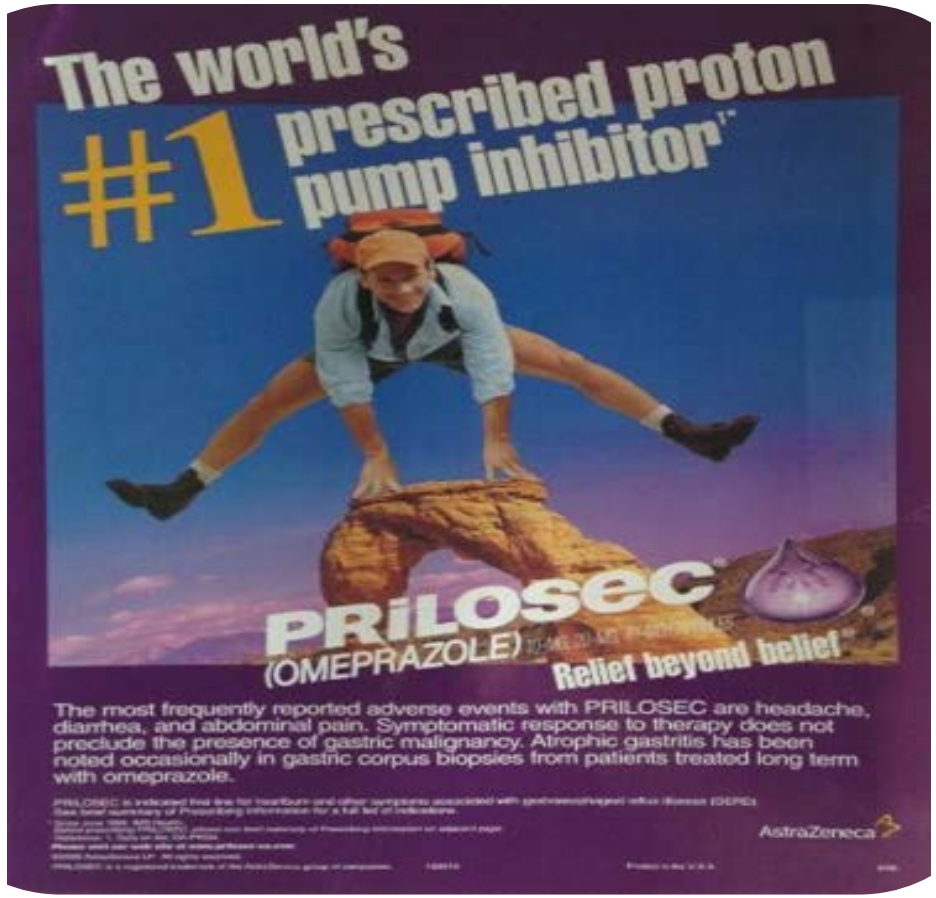

NDC 0173-0695-00
gsk
ADVAIR DISKUS® 100/50
(fluticasone propionate 100 mcg and salmeterol*50 mcg inhalation powder)
FOR ORAL INHALATION ONLY
*Each blister contains 100 mcg of fluticasone propionate and 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base, with lactose.
Federal Law requires the dispensing of ADVAIR DISKUS with the Medication Guide inside the carton.
℞only
100/50
1 DISKUS® Inhalation Device
Containing 1 Foil Strip of 60 Blisters
100/50
ADVAIR DISKUS


NDC 0006-0575-61
7001274700
Janumet®
(sitagliptin and metformin HCl) tablets
50mg/500mg
Dispense the accompanying Medication Guide to each patient.
Each tablet contains 64.25 mg sitagliptin phosphate (equivalent to 50 mg sitagliptin) and 500 mg metformin hydrochloride.
Rx only
60 Tablets
575
Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]
USUAL DOSAGE: See Package Insert.
Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
LOT
EXP.

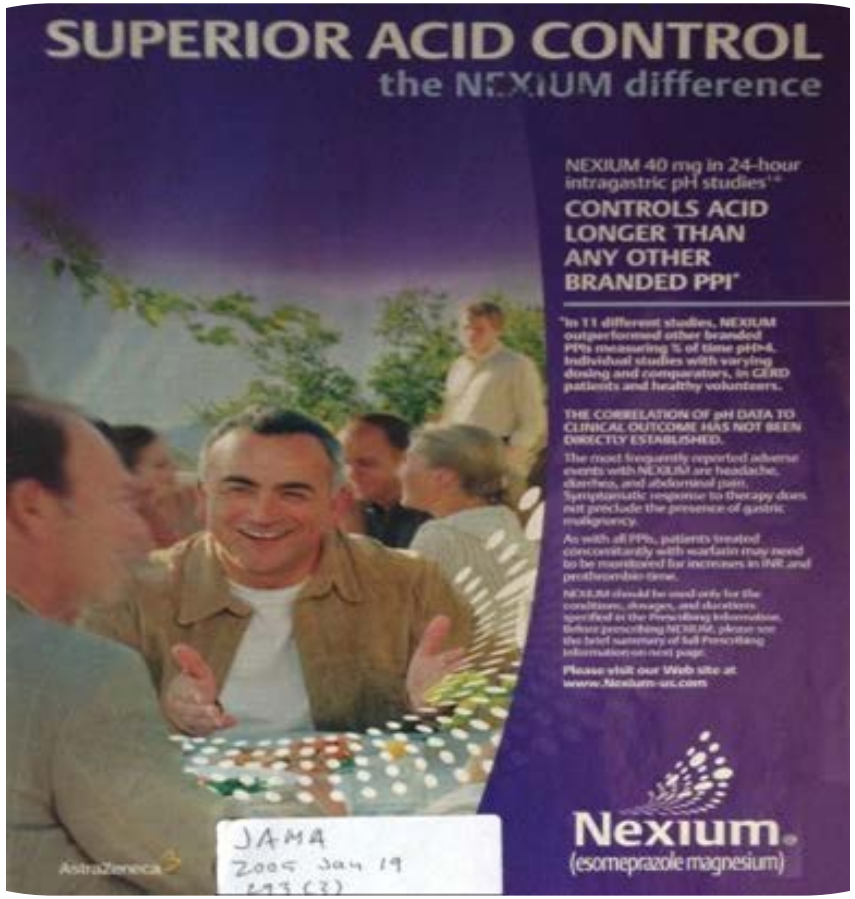
ENANTIOMERS

- Enantiomers are molecules that are mirror images of each other with only one usually being biologically active.
- It has become common practice to introduce a drug as a racemic mixture, which is a mixture of enantiomers.
- Then, when the patent is close to expiring the company releases the active enantiomer as a "new, improved" product.
- A product that begins with "ar" is a right-handed enantiomer.
- A product that that begins with "es" is a left-handed enantiomer.

OMEPRAZOLE



ESOMEPRAZOLE



PROVIGIL
(MODAFINIL)

NUVIGIL
(ARMODAFANIL)

METABOLITES, PRODRUGS and ANALOGS

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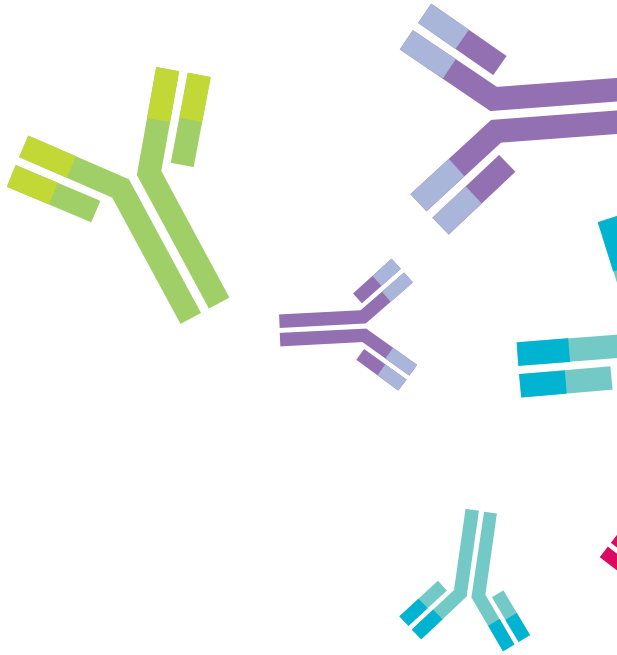
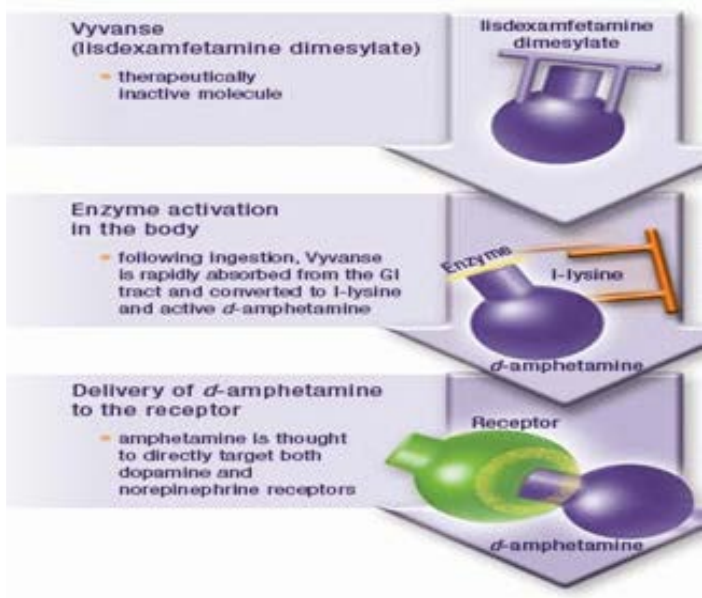
Although there are exceptions, many enantiomers, metabolites, analogs, and prodrugs have no advantages over the originator drug.



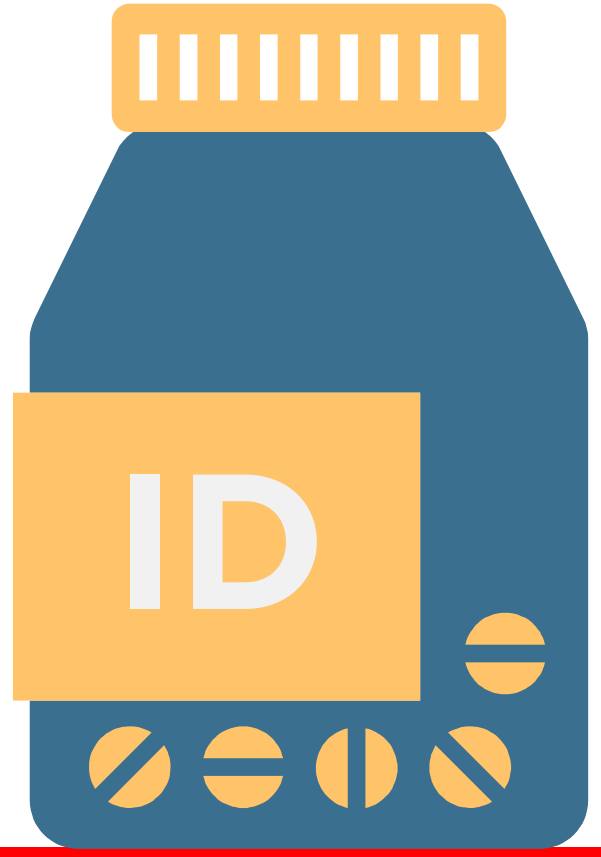
Example **VYVANSE** (*for* ADHD)

- Vyvanse (lisdexamfetamine) is dextroamphetamine linked to a lysine molecule, allowing for it to be cleaved to its components upon ingestion.
- While this peak doses to be reached earlier, there is no advantage to this and could theoretically increase rates of adverse effects.



RENAMING

- **A new indication can extend the patent life of a drug.**
- Some drugs are renamed upon approval for a new indication, allowing for a new trademark. Although this does not affect patent life, a new name prevents substitution of a generic equivalent.



FLUOXETINE

- Fluoxetine is the generic version of both Prozac and Sarafem.
- After Prozac lost patent exclusivity, Sarafem provided new life to the patent, because a pharmacist could substitute generic fluoxetine for Prozac, but not for Sarafem because the indications for which the drugs were approved were different.
- (Now that Sarafem has lost patent exclusivity, both drugs are available as generics.)

PROZAC
fluoxetine hydrochloride

=

Sarafem
fluoxetine hydrochloride

RENAMED DRUGS

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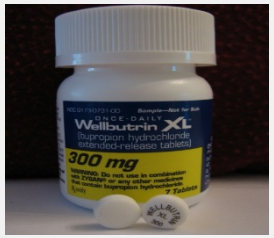
PROZAC fluoxetine hydrochloride	=	Sarafem fluoxetine hydrochloride	=	Fluoxetine
Bupropion	=		=	
	=		=	Sildenafil

COMBINING PROLONGED ACTION WITH RENAMING

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Bydureon is an extended-release form of Byetta. Both are exanatide.

FIRST-IN-CLASS *vs.* ME-TOO DRUGS

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- First-in-class drugs are novel drugs.
- Me-too drugs are similar, related drugs to first-in-class drugs.
- Marketing may exaggerate the benefits of a me-too drug versus the original first-in-class drug.

SIMVASTATIN *and* BAYCOL

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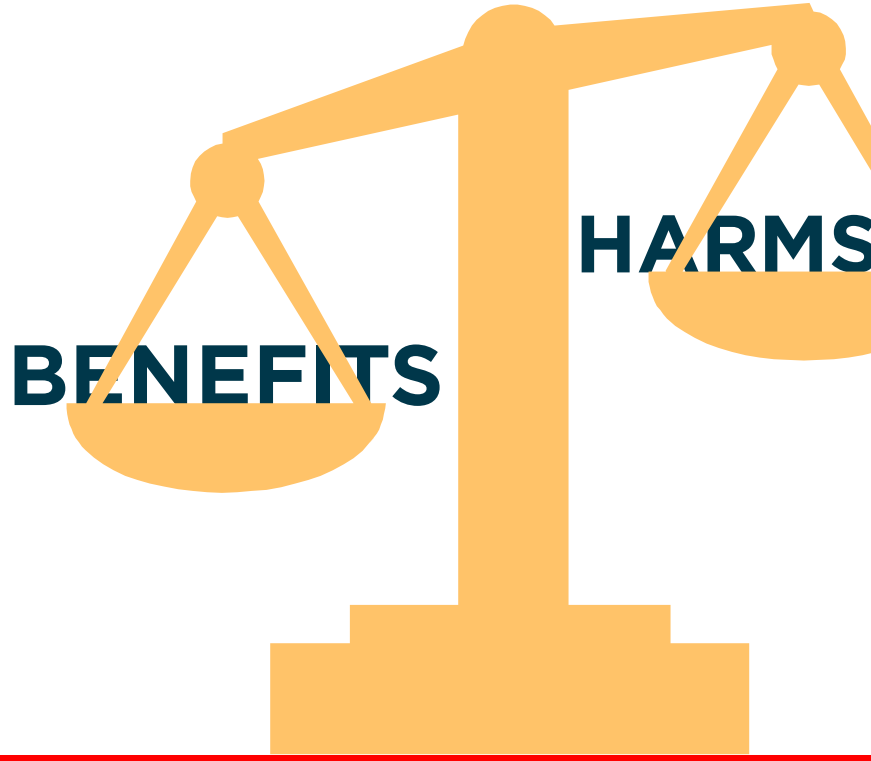
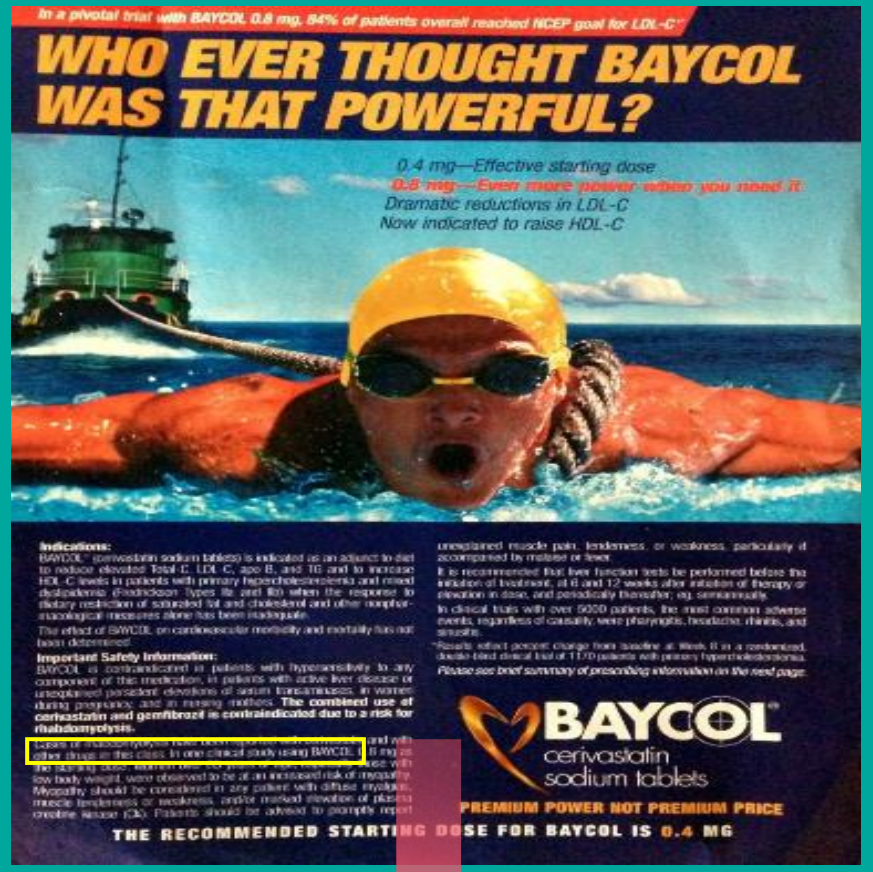
- **Simvastatin**, a me-too drug, is a more effective statin than lovastatin, a first-in-class drug.
- On the other hand, Baycol (**cerivastatin**) was withdrawn from the market due to a disproportionate number of cases of rhabdomyolysis.



NEJM, January 1999

"**Rare cases** of rhabdomyolysis have been reported with cerivastatin"

NEJM, January 2001



"**Cases** of rhabdomyolysis have been reported with cerivastatin"

me-too drugs: MARKETING MESSAGES

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- Increased potency or longer duration of effect
- Faster onset of action
- Fewer unwanted effects
- Improved receptor selectivity

Conversely, first-in-class drugs may market their longer history and larger body of research.

INCREASED POTENCY *or* LONGER DURATION *of* EFFECT

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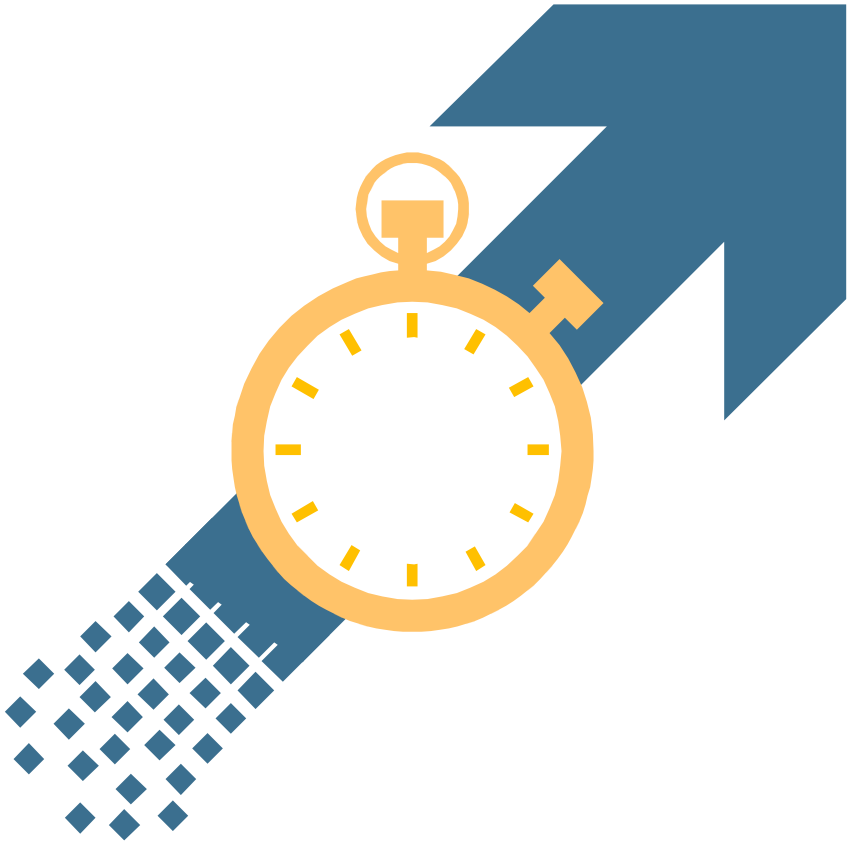
- May add no clinical benefit
- May increase the risk of adverse events
- May increase flexibility in dosing options



FASTER ONSET OF ACTION

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In chronically used drugs, such as statins, faster onset of action would only affect the first dose.

FEWER UNWANTED EFFECTS

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- Unwanted effects take time to be discovered and reported.
- Pre-market studies cannot pick up long-term adverse effects, drug interactions, or effects that occur only in elders, diabetics, or other subpopulations.
- Claims of increased safety for new drugs are not trustworthy without long-term data.

IMPROVED RECEPTOR SELECTIVITY

Molecular stories, such as improved receptor selectivity, may not necessarily have a clinical benefit.

The importance of
ADS IN MEDICAL JOURNALS

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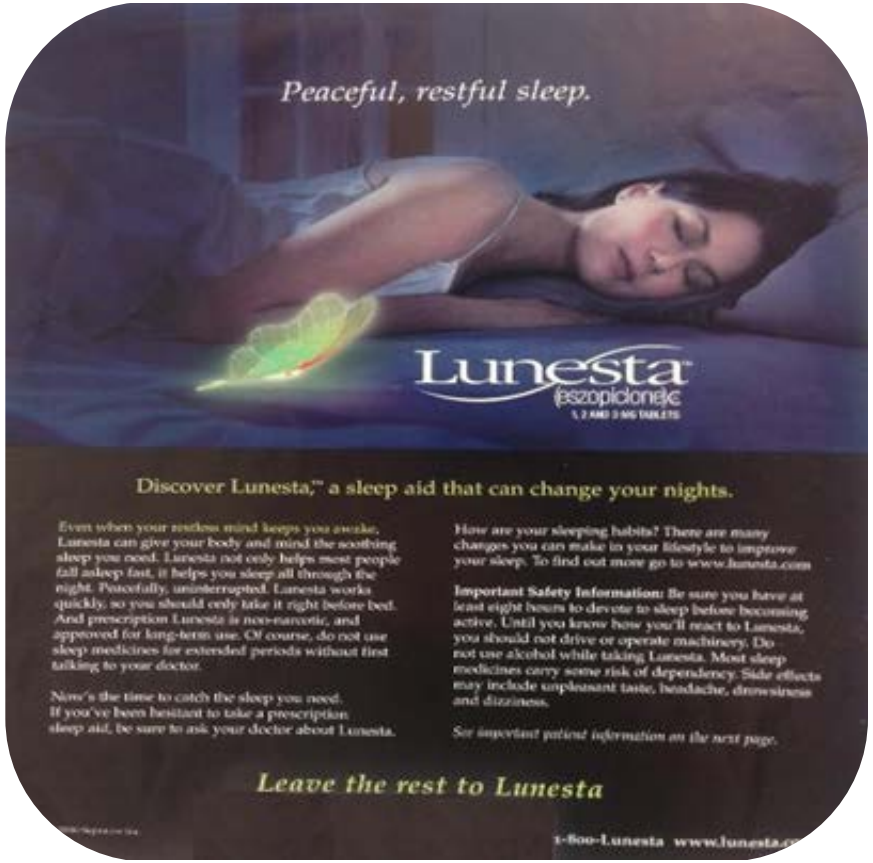
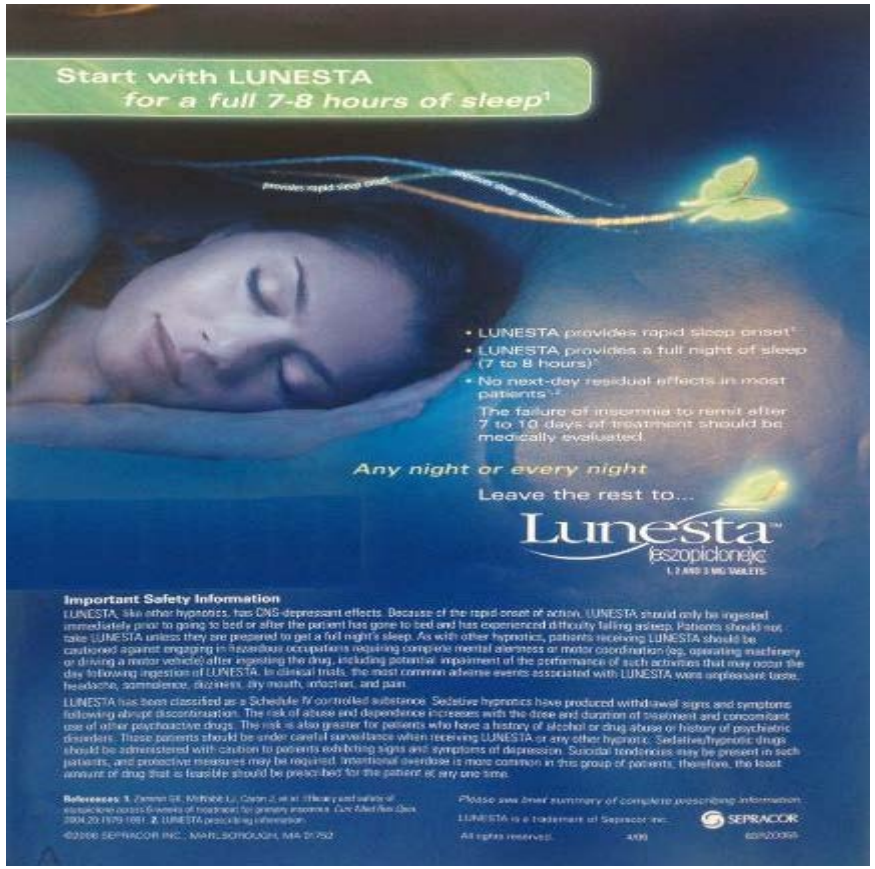
Ads in medical journals:

- Are an important part of promotional campaigns.
- Reinforce marketing messages conveyed by drug reps, direct mail, and speaker programs.
- Provide reminders that retain drug names in our subconscious.
- Reinforce direct-to-consumer-advertising (DTCA) via coordination of product logos, colors, and symbols.

CONSUMER
advertisement



MEDICAL JOURNAL
advertisement



INFORMATION IN ADS IS NOT ACCURATE

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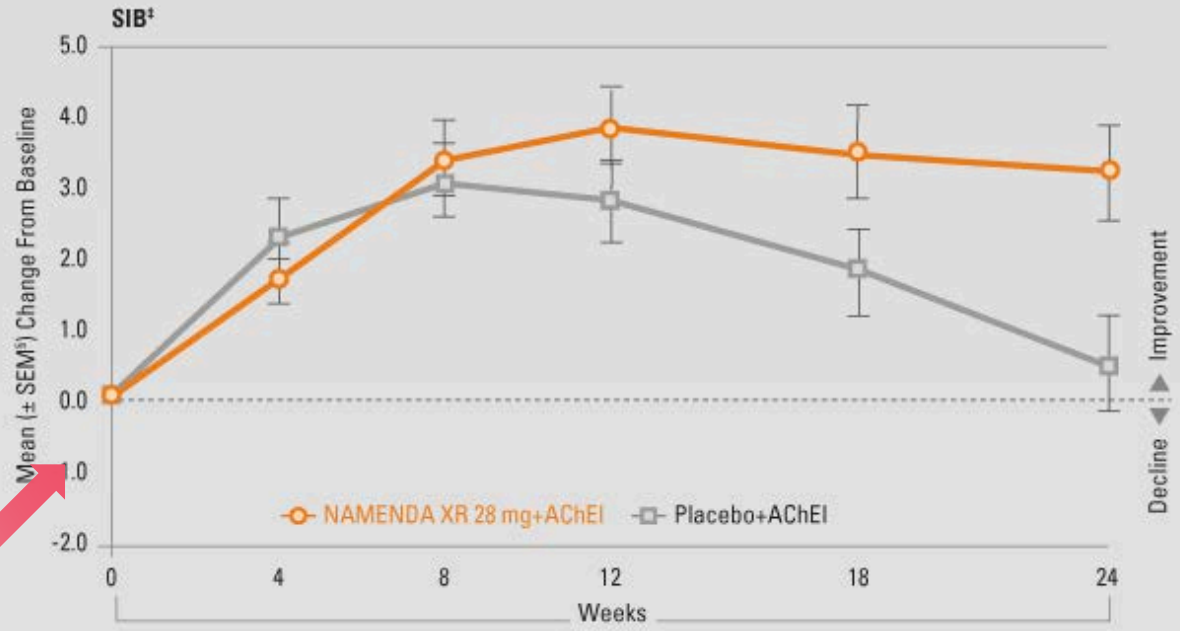
- One-third of pharmaceutical ads are scientifically inaccurate. (Wilkes, 1992)
- Graphs can be misleading. (Cooper, 2003)
  - 26% of graphs had numeric distortion.
  - One-third contained design features that distorted the data depicted.
  - Only 58% presented an outcome relevant to the drug's indication.
  - Only 4% contained confidence intervals.

Example:

NUMERIC DISTORTION

*Note the range of the y-axis {0-5} on a 100-point scale

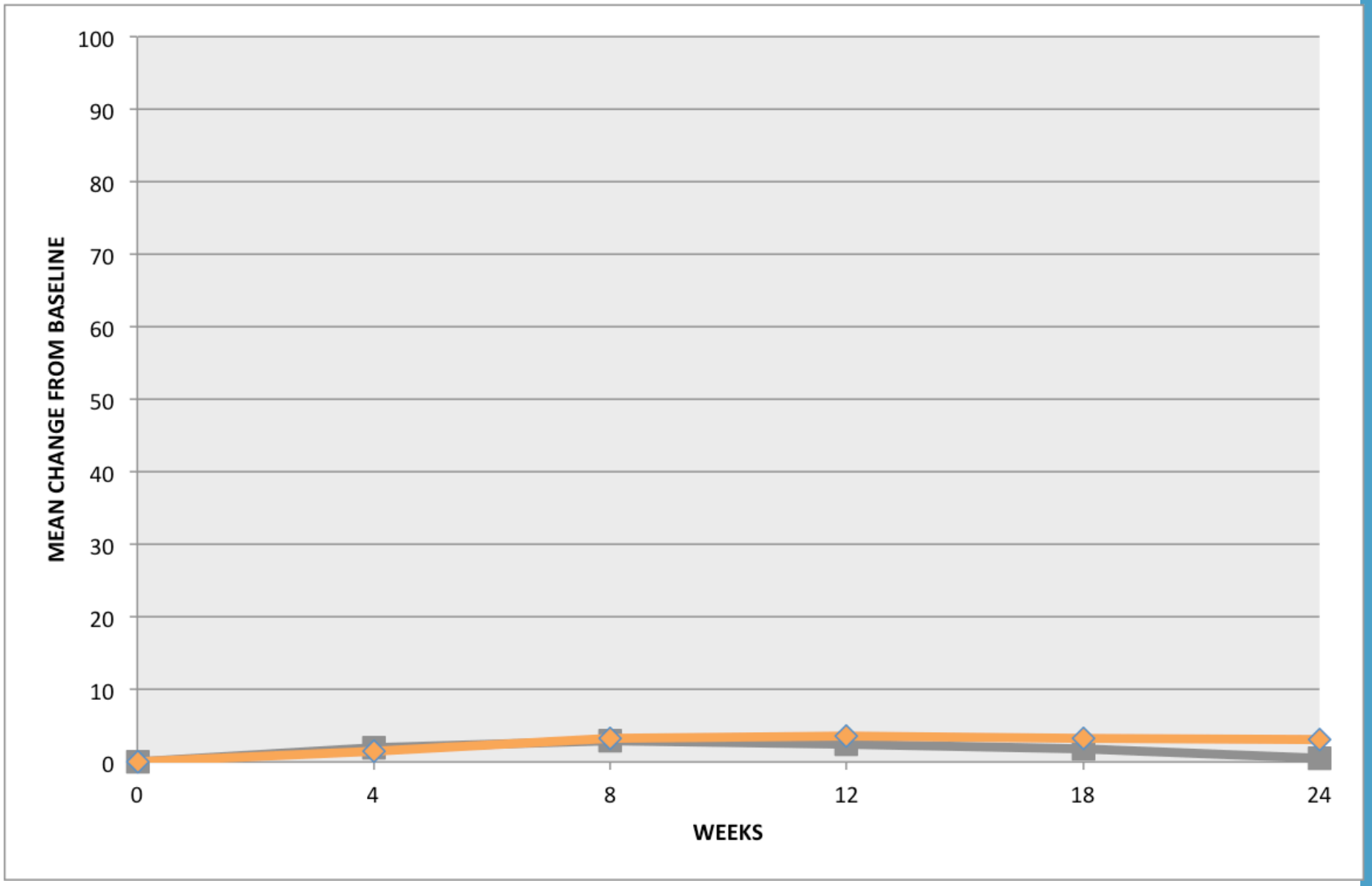
Combination therapy with NAMENDA XR 28 mg+AChEI* demonstrated greater improvement in cognition vs placebo+AChEI treatment at 24 weeks, using an LOCF† analysis[1]



Study Description: Results of a randomized, multicenter, double-blind, placebo-controlled, parallel-group, multinational study investigating the efficacy of NAMENDA XR in outpatients with moderate to severe Alzheimer's disease (AD). The study involved 677 patients with probable AD, ≥50 years of age, with a Mini-Mental State Examination (MMSE) score of ≥3 to ≤14 points, who were on a stable dose of an AChEI (donepezil, rivastigmine, or galantamine) for a minimum of 3 months prior to study entry and should have remained on the same dose throughout the study. Patients were randomized (1:1) to receive NAMENDA XR (n=342; 28 mg QD) or placebo (n=335) for 24 weeks; 545 patients (273 NAMENDA XR, 272 placebo) completed the study. Primary efficacy measures were changes from baseline on the Severe Impairment Battery (SIB) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). Primary data analyses were performed using the LOCF approach for missing data; results were also analyzed using the observed cases (OC) approach. The figure above shows the time course of the change from baseline in SIB score for patients completing 24 weeks of treatment. The SIB examines selected aspects of cognitive performance, including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment.[2,3]

Compare:

WITH THE SAME RESULTS ON A 100-POINT SCALE



ADS *and* OTHER PROMOTION must:

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- Be consistent with the FDA-approved label
- Contain truthful information
- Not contain assertions that can't be proven
- Not overstate effectiveness
- Not minimize or omit risks
- Not promote off-label uses (uses that are not in accordance with FDA - approved labeling)

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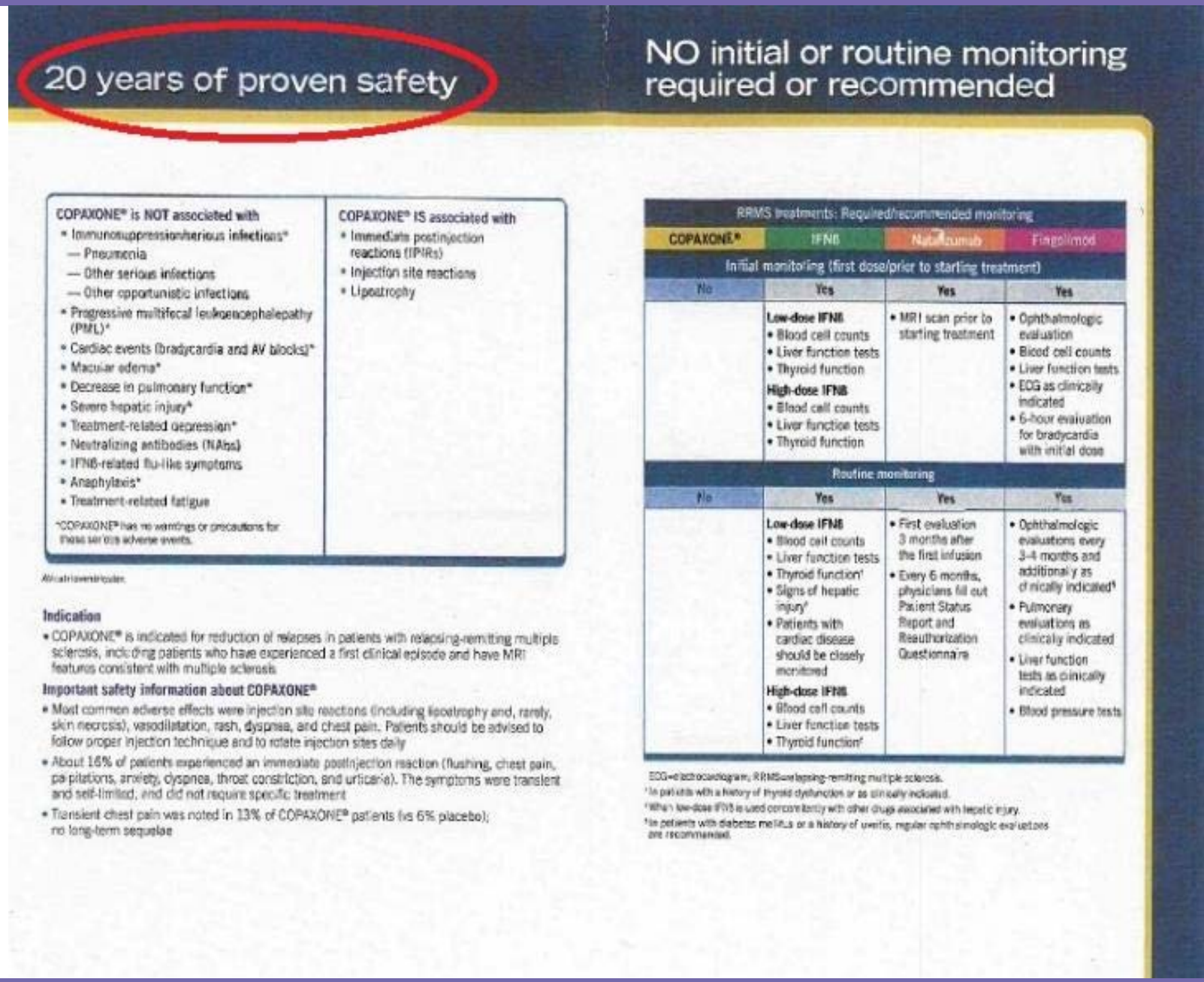
MISLEADING PROMOTION

A misleading professional exhibit panel for copaxone (glatiramer- acetate) at an American academy of neurology conference



20 years of proven safety

NO initial or routine monitoring required or recommended

COPAXONE® is NOT associated with*	COPAXONE® IS associated with
• Immunosuppression/serious infections* — Pneumonia — Other serious infections — Other opportunistic infections • Progressive multifocal leukoencephalopathy (PML)* • Cardiac events (bradycardia and AV blocks)* • Macular edema* • Decrease in pulmonary function* • Severe hepatic injury* • Treatment-related depression* • Neutralizing antibodies (NAbs) • IFNß-related flu-like symptoms • Anaphylaxis* • Treatment-related fatigue	• Immediate postinjection reactions (IPIRs) • Injection site reactions • Lipoatrophy

*COPAXONE® has no warnings or precautions for these serious adverse events.

Indication

- COPAXONE® is indicated for reduction of relapses in patients with relapsing-remitting multiple sclerosis, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Important safety information about COPAXONE®

- Most common adverse effects were injection site reactions (including lipoatrophy and, rarely, skin necrosis), vasodilatation, rash, dyspnea, and chest pain. Patients should be advised to follow proper injection technique and to rotate injection sites daily.
- About 16% of patients experienced an immediate postinjection reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria). The symptoms were transient and self-limited, and did not require specific treatment.
- Transient chest pain was noted in 13% of COPAXONE® patients (vs 6% placebo); no long-term sequelae.

RRMS treatments: Required/recommended monitoring

	COPAXONE®	IFNß	Natalizumab	Fingolimod
Initial monitoring (first dose/prior to starting treatment)	No	Yes	Yes	Yes
		Low-dose IFNß • Blood cell counts • Liver function tests • Thyroid function **High-dose IFNß** • Blood cell counts • Liver function tests • Thyroid function	• MRI scan prior to starting treatment	• Ophthalmologic evaluation • Blood cell counts • Liver function tests • ECG as clinically indicated • 6-hour evaluation for bradycardia with initial dose
Routine monitoring	No	Yes	Yes	Yes
		Low-dose IFNß • Blood cell counts • Liver function tests • Thyroid function† • Signs of hepatic injury‡ • Patients with cardiac disease should be closely monitored **High-dose IFNß** • Blood cell counts • Liver function tests • Thyroid function†	• First evaluation 3 months after the first infusion • Every 6 months, physicians fill out Patient Status Report and Reauthorization Questionnaire	• Ophthalmologic evaluations every 3–4 months and additionally as clinically indicated§ • Pulmonary evaluations as clinically indicated • Liver function tests as clinically indicated • Blood pressure tests

ECG=electrocardiogram; RRMS=relapsing-remitting multiple sclerosis.
†In patients with a history of thyroid dysfunction or as clinically indicated.
‡When low-dose IFNß is used concomitantly with other drugs associated with hepatic injury.
§In patients with diabetes mellitus or a history of uveitis, regular ophthalmologic evaluations are recommended.

OVERSTATEMENT OF EFFICACY

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The Exhibit Panel states: ***"20 years of proven safety."***

FDA Comments:

- Long term… safety and efficacy… has not been demonstrated by substantial evidence or substantial clinical experience. The CLINICAL STUDIES section of the PI only includes data for up to three years in duration.

OMISSION OF RISK INFORMATION

COPAXONE® is NOT associated with

- Immunosuppression/serious infections*
  - — Pneumonia
  - — Other serious infections
  - — Other opportunistic infections
- Progressive multifocal leukoencephalopathy (PML)*
- Cardiac events (bradycardia and AV blocks)*
- Macular edema*
- Decrease in pulmonary function*
- Severe hepatic injury*
- Treatment-related depression*
- Neutralizing antibodies (NAbs)
- IFNß-related flu-like symptoms
- Anaphylaxis*
- Treatment-related fatigue

*COPAXONE® has no warnings or precautions for these serious adverse events.

COPAXONE® IS associated with

- Immediate postinjection reactions (IPIRs)
- Injection site reactions
- Lipoatrophy

COPAXONE:
OMISSION OF INFORMATION

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The Exhibit Panel states "Copaxone is NOT associated with immunosuppression/serious infections, decrease in pulmonary function, or anaphylaxis."

FDA Comments:

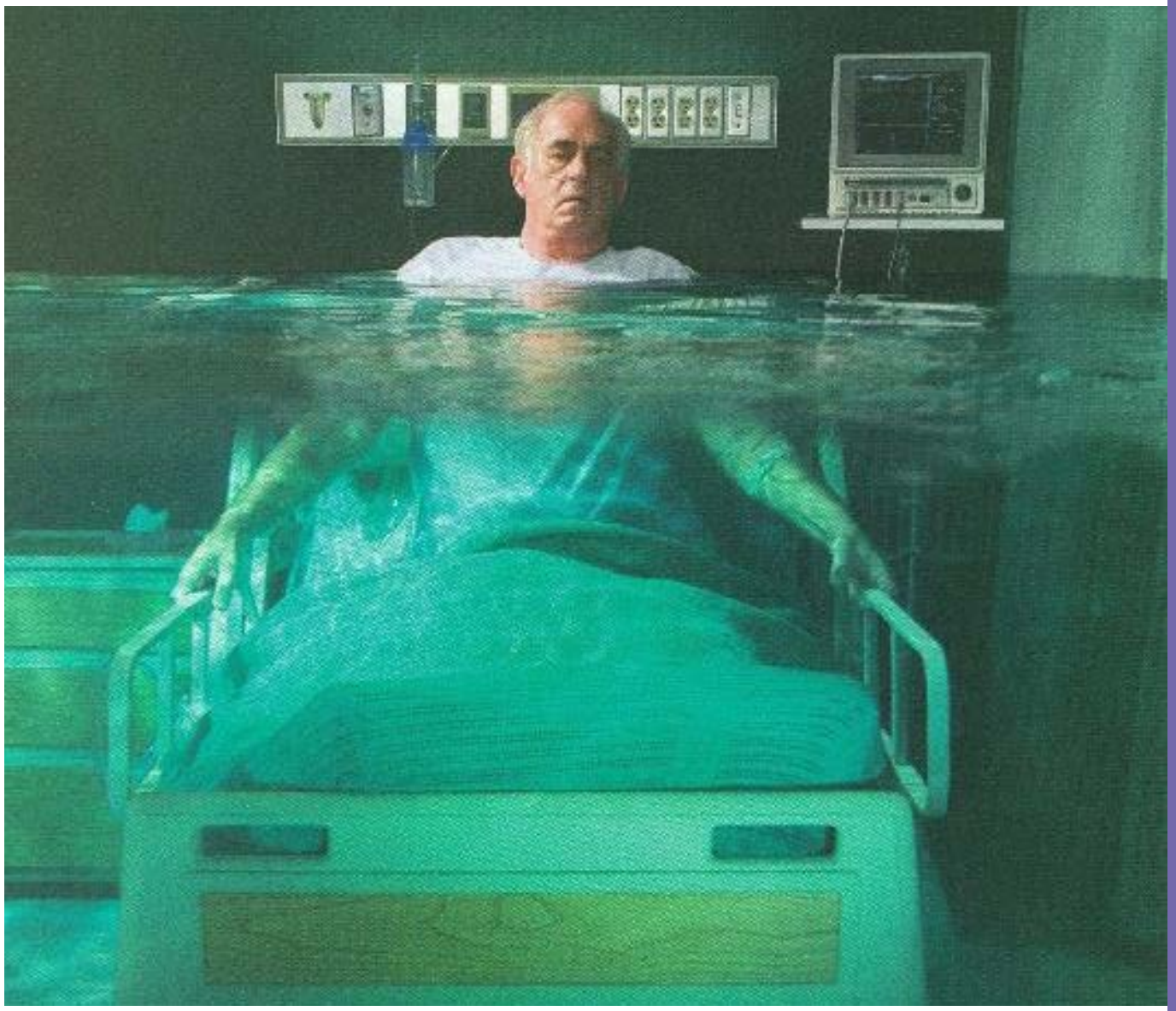
- The table suggests that Copaxone is not associated with immunosuppression/infections, pulmonary function, and anaphylaxis/hypersensitivity, when this is not the case.
- The table fails to present the Warnings for chest pain, skin necrosis and… effects… on immune response.

Intravenous
B-type natriuretic peptide (BNP)

NATRECOR®

(nesiritide)

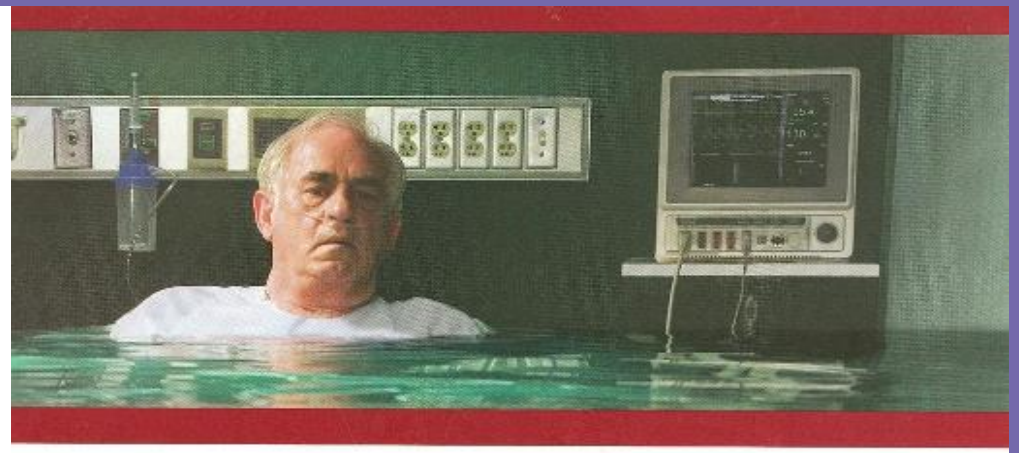
The image seems to imply that Natrecor can prevent death.



Indication

NATRECOR® (nesiritide) is indicated for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. In this population, the use of NATRECOR® reduced pulmonary capillary wedge pressure and improved dyspnea.

Natrecor is ONLY indicated for the symptomatic relief of dyspnea in patients with acutely decompensated CHF.



Indication

NATRECOR® (nesiritide) is indicated for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. In this population, the use of NATRECOR® reduced pulmonary capillary wedge pressure and improved dyspnea.

The **recommended dose** of NATRECOR® is an intravenous bolus of 2 mcg/kg followed by a continuous infusion of 0.01 mcg/kg/min.

IMPORTANT SAFETY INFORMATION

HYPOTENSION

NATRECOR® may cause hypotension and should be administered only in settings where blood pressure can be monitored closely. If hypotension occurs during administration of NATRECOR®, the dose should be reduced or discontinued. At the **recommended dose** of NATRECOR®, the incidence of symptomatic hypotension (4%) was similar to that of IV nitroglycerin (5%). Asymptomatic hypotension occurred in 8% of patients treated with either drug. In some cases, hypotension that occurs with NATRECOR® may be prolonged. The mean duration of symptomatic hypotension was longer with NATRECOR® than IV nitroglycerin (2.2 versus 0.7 hours, respectively).

NATRECOR® should not be used in patients with systolic blood pressure <90 mm Hg or as primary therapy in patients with cardiogenic shock. The rate of symptomatic hypotension may be increased in patients with a baseline blood pressure <100 mm Hg, and NATRECOR® should be used cautiously in these patients. In earlier trials, when NATRECOR® was initiated at doses higher than the 2 mcg/kg bolus followed by a 0.01 mcg/kg/min infusion, the frequency, intensity, and duration of hypotension were increased. The hypotensive episodes were also more often symptomatic and/or more likely to require medical intervention.

NATRECOR® is not recommended for patients for whom vasodilating agents are not appropriate and should be avoided in patients with low cardiac filling pressures.

RENAL

NATRECOR® may affect renal function in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with NATRECOR® may be associated with azotemia. In the VMAC trial, through day 30, the incidence of elevations in creatinine to >0.5 mg/dl above baseline was 28% and 21% in the NATRECOR® and nitroglycerin groups, respectively. When NATRECOR® was initiated at doses higher than 0.01 mcg/kg/min, there was an increased rate of elevated serum creatinine over baseline compared with standard therapies, although the rate of acute renal failure and need for dialysis was not increased.

MORTALITY

In seven NATRECOR® clinical trials, through 30 days, 5.5% in the NATRECOR® treatment group died as compared with 4.3% in the group treated with other standard medications. In five clinical trials, through 180 days, 21.5% in the NATRECOR® treatment group died as compared with 20.7% in the group treated with other medications. There is not enough information to know about the effect of NATRECOR® on mortality.

References: 1. NATRECOR® Full Prescribing Information. **2.** Data on file, Scios Inc. **3.** Publication Committee for the VMAC Investigators. JAMA. 2002;287:1531-1540. **4.** Elkayam U. Circulation. 2005;112(suppl II):II-673-II-676. Abstract 3168.

Intravenous
B-type natriuretic peptide (BNP)
NATRECOR®
(nesiritide)

THE FDA OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

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- The FDA's Office of Prescription Drug Promotion (OPDP) regulates prescription drug advertising and other forms of marketing.
- However, ads are not pre-approved and the FDA lacks personnel to assess all of the marketing material it receives.

FDA'S "BAD AD" PROGRAM

- Launched in 2010 to educate healthcare providers about the role they can play in helping make sure that prescription drug advertising is truthful and not misleading.
- Provides an easy way to report misleading information to the agency:
  - E-mail BadAd@FDA.gov or call 855-RX-BADAD.
  - To learn more, go to www.FDA.gov/BadAd.

FDA'S "BAD AD" PROGRAM

- Although prescription drug advertisements must be sent to the FDA, they are not cleared by the FDA before being disseminated. The FDA cannot examine every ad.
- The FDA cannot monitor sales representatives, industry-sponsored dinner and speaker presentations.
- Healthcare providers should report any misleading information that is provided in advertisements, by drug reps, or in presentations.

your RESPONSIBILITY

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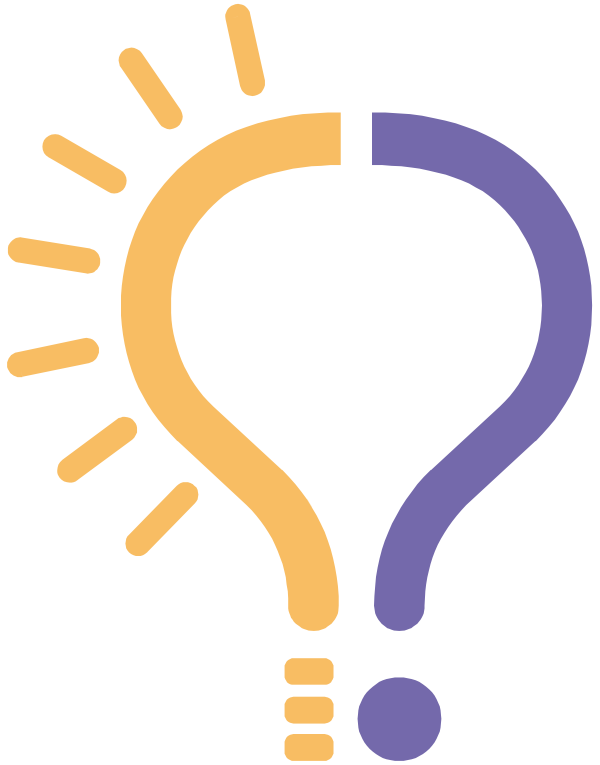
- Once a drug is approved, the FDA has limited resources to monitor adverse events and promotion.
- The FDA depends on healthcare providers to report adverse events and misleading promotion.
- Healthcare professionals consider it part of their professional responsibility to report adverse events to MedWatch and report misleading promotion (in the form of ads, sales presentations, or industry-sponsored events) to BadAds.



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MORE RESOURCES

Please visit DCRx for more information on these and other treatment-related subjects.

doh.dc.gov/dcrx