Policy and Enforcement Update from DDMAC

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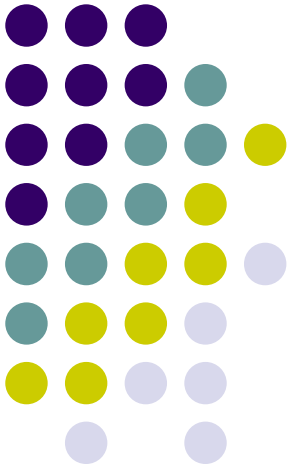
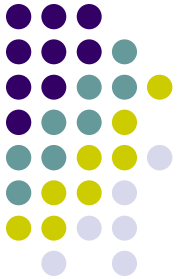
Food and Drug Administration
October 1, 2009



Topics



- Policy Update
  - Draft guidances
  - DTC FDAAA Provisions
  - Future guidance development
- Enforcement Update and Analysis

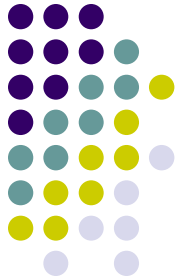
Draft Risk Presentation Guidance

- Presenting Risk Information in Prescription Drug and Medical Device Promotion
- Issued May 2009

Draft Risk Presentation Guidance

- Scope and Objective
  - Guidance focuses on the presentation of risk information in prescription drug promotion (ads and promotional labeling), restricted medical device ads, and promotional labeling for all medical devices
  - Objective is to aid industry in effectively communicating risk information in their promotion to **both** healthcare professionals and consumers
  - It is critically important to disclose risk information appropriately and effectively in promotional materials

Draft Risk Presentation Guidance

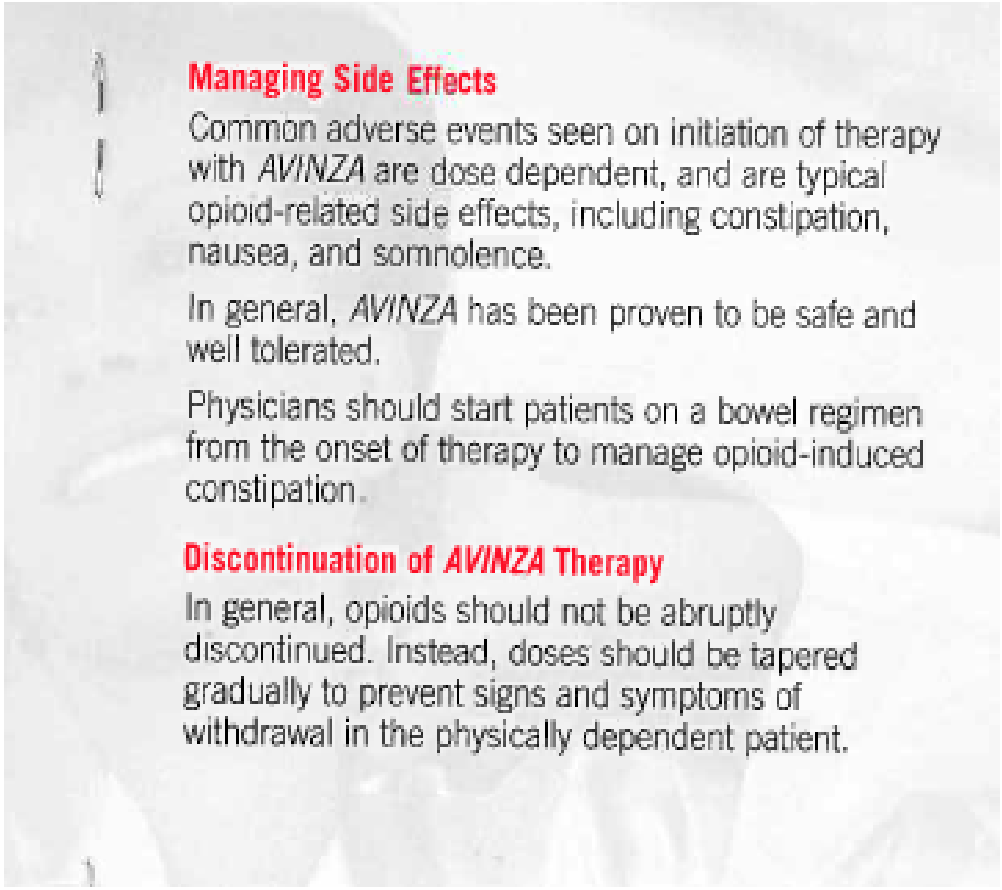


- Omission or minimization of risk information is the most frequently cited violation in Agency advertising and promotion regulatory letters
- Research on Rx drug promotion has shown that majority of consumers
  - Believe that ads do not provide enough risk info
  - Often, after viewing ads, do not understand who should and should not use the drug
  - Do not understand the possible risks of the drug
- Guidance describes factors FDA considers when reviewing risk communication in pieces – goal is to help industry gain a better understanding of what they should consider as they develop promotional pieces

Overview

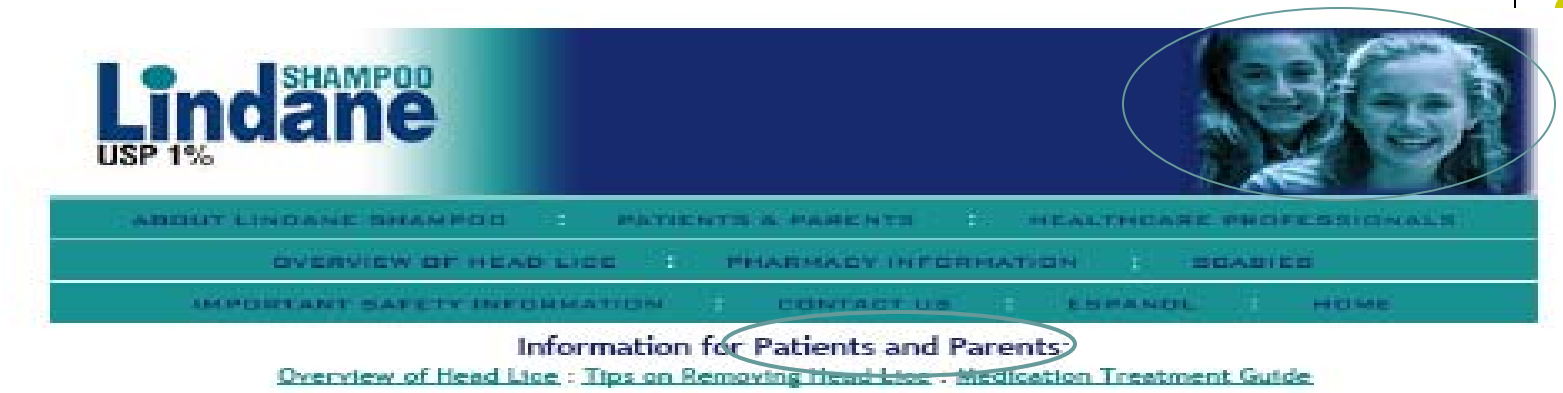
- Guidance discusses both content and format factors relevant to FDA's determination of whether promotional materials adequately present risk information
  - FDA relies on a vast scientific body of knowledge regarding human cognition in assessing which factors to consider
  - FDA looks not just at specific risk-related statements, but also at the net impression – i.e., the message communicated by all the elements of the piece as whole – in determining whether the product's risks and benefits are fairly and accurately communicated
  - Guidance provides numerous examples of what does, and does not, constitute fair and balanced presentation of risk information

Recommendations and Examples



- A promotional piece that communicates a product's benefits should similarly communicate the most serious and most frequently occurring risks involved in using the product
- In this case, the file card misleadingly failed to disclose any of the serious or life threatening risks that can be caused by Avinza

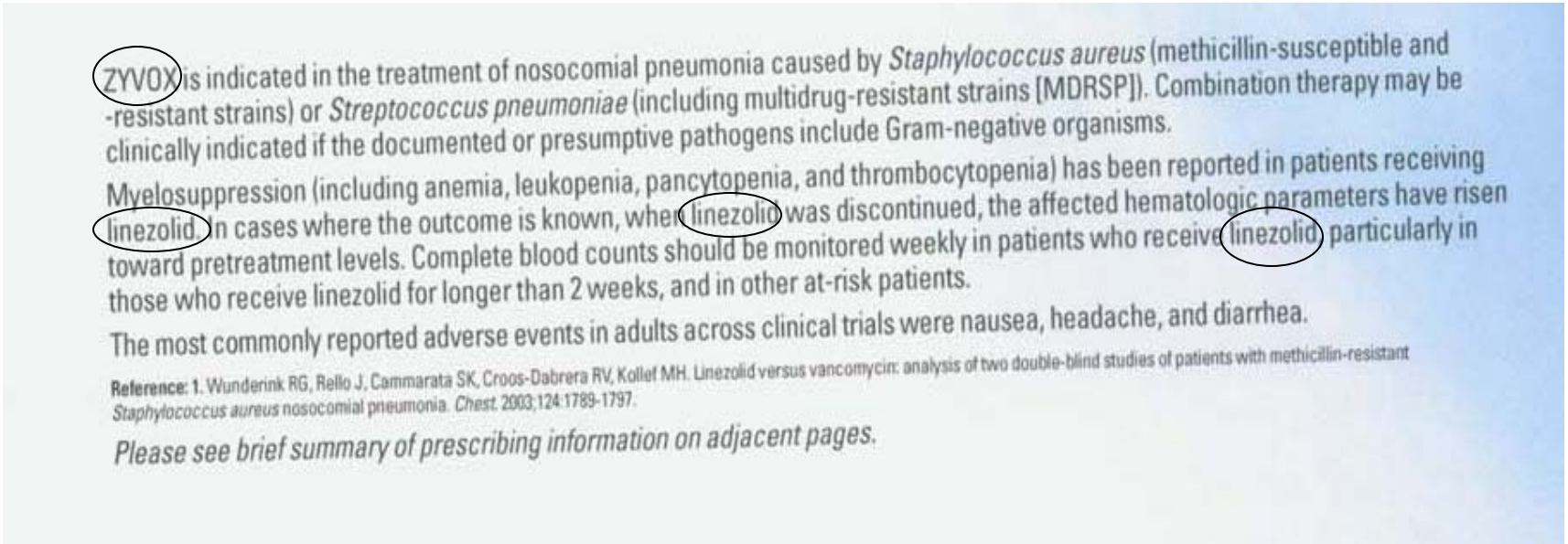
Recommendations and Examples



- A piece promoting use of a product in a selected class of patients should convey the side effects especially applicable to that selected class of patients
- The web page completely omitted the risks associated with use of Lindane Shampoo in children
  - Lindane's PI includes a Boxed Warning re: need for caution when used in children due to risk of serious neurotoxicity (including seizures and death)

Recommendations and Examples

- Risk information should be presented in the same terms and with the same degree of specificity as benefit information
  - If benefit information is presented in consumer-friendly language, risk information should also be in **consumer-friendly language**
  - If a piece refers to the product by brand name when presenting efficacy information, it should do the same for risk information



ZYVOX is indicated in the treatment of nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP]). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than 2 weeks, and in other at-risk patients.

The most commonly reported adverse events in adults across clinical trials were nausea, headache, and diarrhea.

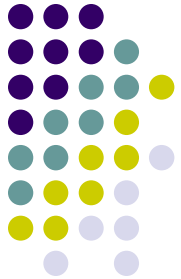
Reference: 1. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid versus vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest.* 2003;124:1789-1797.

Please see brief summary of prescribing information on adjacent pages.

Recommendations & Examples

- Quantity of information
  - As the amount of benefit information conveyed in the piece increases, the amount of risk information conveyed in the piece should similarly increase
  - If benefit information is easily understood and remembered through repetition or other techniques, risk information should be similarly reinforced

Guidance Location & Comments

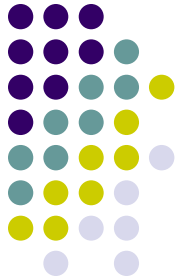


- Guidance is available online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf
- Comment period closed August 25th; general comments on Agency guidances are welcome at any time
- Docket No. FDA-2008-D-0253; (electronic comments can be viewed under Docket No. above at http://www.regulations.gov)

Draft Brief Summary Guidance

- Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements
- Analyzing data from Brief Summary studies
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069984.pdf

Title IX of FDAAA – DTC provisions

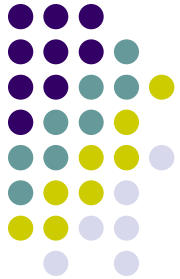


- Sec. 901 of Title IX of FDAAA contains a number of provisions related to DTC advertising:
  - Prereview of DTC TV ads (adds § 503B to FDCA)
  - Clear, conspicuous, and neutral manner major statement requirement (amends § 502(n) of FDCA)
  - Civil monetary penalties for violative DTC ads (amends § 303 of FDCA)
  - Report on DTC advertising
- Sec. 906 of Title IX - Statement for Inclusion in DTC Drug Ads

Activities to Implement FDAAA

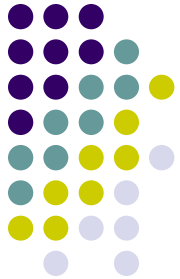
- Per FDAAA, Agency must report to Congress on DTC advertising's ability to communicate to population subsets, including the elderly, children, and racial and ethnic minority communities
  - Report to be submitted to Congress
- Per FDAAA, Agency must by regulation establish standards to determine whether a major statement is presented in the required "clear, conspicuous, and neutral manner"
  - Proposed rule to be issued next year
- Per FDAAA, Agency must study whether toll-free adverse event reporting statement is appropriate to include in TV ads
  - Revised study design published in Federal Register on August 18, 2009 for public comment
    - Notice can be viewed at www.regulations.gov (Docket FDA–2008–N–0595)
  - Comment period closed September 17, 2009

Future Policy Development



- Identifying areas for future guidance development
- Allocating more resources into policy and guidance development
- Interested in what our stakeholders believe are important areas to address
  - Interest in promotion on internet and use of social media in promotion

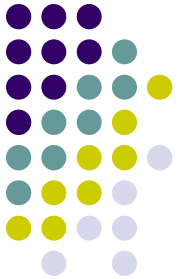
Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools



- November 12-13, 2009
- National Transportation and Safety Board
- Comments due February 28, 2010
- To Register: Go to www.regulations.gov, search by the docket number (FDA2009N0441), and click on the "Actions" menu to the far right to register

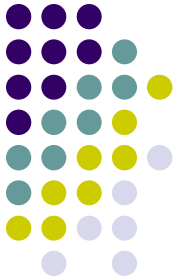
Enforcement

Enforcement Numbers and Breakdown for January 1, 2009 – September 25, 2009



- Number of Regulatory Letters
  - 33 Total Letters
    - 10 Warning Letters
    - 23 Untitled Letters
- Previous Years
  - 2008: 21 Letters
  - 2007: 19 Letters
  - 2006: 22 Letters

Promotional Vehicles Cited Include



- Consumer DVDs and webcast videos
- Promotional videos on cnn.com and youtube.com
- Online banners
- Sponsored links
- Sales reps' activities
- Promotion in commercial exhibit halls
- Pharmacy formulary flashcard
- Medical convention post meeting news ad
- Mailers to healthcare professionals

Most Common Violations Occurring in 2009

- Omission and minimization of risk information
- Promotion of unapproved uses and broadening the indications of drugs
- Misleading claims of efficacy

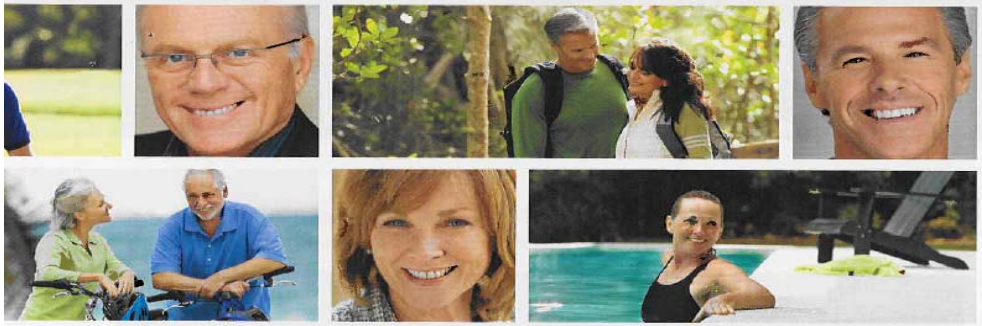
Bystolic Warning Letter

- 8-Page Launch Journal Ad
- Violations
  - Unsubstantiated superiority claims
  - Omission and minimization of risks
  - Unsubstantiated efficacy claims
- Indication
  - Treatment of hypertension and may be used alone or in combination with other BP agents

For the treatment of hypertension

Introducing a novel beta blocker for a broad range of patients.

NEW
Bystolic™
(nebivolol)
Next generation beta blocker



- Unique mechanism of action includes cardioselective beta blockade and vasodilation[1*]
- Significant BP reductions as monotherapy and in combination[1-3]
- Effective across a broad range of patients[1-3]
- Favorable tolerability profile with a low incidence of beta blocker related side effects[1,2]
- Once-daily antihypertensive with efficacy maintained over 24 hours[1]

*In extensive metabolizers (most of the population) and at doses ≤10 mg, BYSTOLIC is preferentially β_1 selective. The mechanism of action of the antihypertensive response of BYSTOLIC has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity, and (5) vasodilation and decreased peripheral vascular resistance.

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

NEW
Bystolic™
(nebivolol)
Next generation beta blocker

A unique mechanism of action

Unique mechanism of action includes cardioselective beta blockade and vasodilation[1*]

BYSTOLIC

Cardioselectivity[1]

Vasodilation[1†]

Additional properties:

Suppression of renin activity and diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers[1]

*In extensive metabolizers (most of the population) and at doses ≤10 mg, BYSTOLIC is preferentially β_1 selective. The mechanism of action of the antihypertensive response of BYSTOLIC has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity, and (5) vasodilation and decreased peripheral vascular resistance.

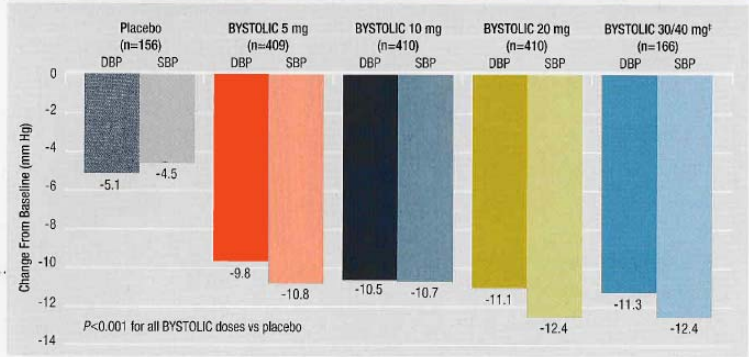
†Vasodilation occurs independently from α_1 blockade.

Efficacy as monotherapy and in combination

In 3-month studies

BYSTOLIC monotherapy achieves significant BP reductions[1,2]

Reductions From Baseline in Mean Sitting DBP and SBP at Trough at 3 Months[2]



Pooled results from two U.S. phase III, 3-month, placebo-controlled studies of BYSTOLIC monotherapy for the treatment of mild to moderate hypertension. Primary endpoint was sitting DBP at trough. Mean values at baseline: sitting DBP at trough, 99.3 mm Hg; sitting SBP at trough, 152.4 mm Hg (N=1716).

†Patients randomized to the 30/40 mg treatment arm initiated treatment with BYSTOLIC 30 mg and were then titrated to 40 mg if the 30 mg dose was tolerated (ie, heart rate >55 beats per minute).

Efficacy demonstrated across a broad range of patients[1,2]

- Studies included the following hypertensive patient populations: 42% obese (BMI ≥30 kg/m^2), 6% poor metabolizers, 20% aged 65 years or older, 45% female, 14% Black, and 7% diabetic[2]

BYSTOLIC achieves significant heart rate reductions[2]

- Demonstrated consistent and effective beta blockade[1,2]

In a 3-month combination therapy study§

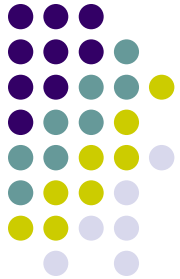
Additional BP reductions for patients needing add-on therapy[2]

- Significant DBP and SBP reductions when BYSTOLIC was added to ACEIs, ARBs, and/or diuretics[2]

§Results from a 3-month randomized, double-blind, placebo-controlled study to assess the efficacy and safety of BYSTOLIC as add-on therapy to 1 or 2 other antihypertensives (ACEIs, ARBs, and/or diuretics).

NEW
Bystolic™
(nebivolol)
Next generation beta blocker

Contact information



- **NEW** Web address:
  - http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm (main DDMAC site)
  - Phone: 301-796-1200
  - DDMAC Regulatory information site:
    - http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm109905.htm
- Address for submissions:
  - Division of Drug Marketing, Advertising and Communications
  - Food and Drug Administration
  - Center for Drug Evaluation and Research
  - 5901-B Ammendale Road
  - Beltsville, MD 20705-1266