SECOND ANNUAL PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

March 15, 2011 ■ Silver Spring, MD

Co-sponsored by

Outcomes Targeted for Labeling: What Works and What Doesn't?

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FDA

Outcomes and Labeling: Overview

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Laurie Burke

PRO Consortium history

- Beyond PROs

Outcomes claims in labeling

- History
- Definitions
- Evidence
- Examples

Outcomes NOT in labeling—why not?

Next steps to improve claims in labeling

Marc Walton

Nomenclature and classification framework for outcomes assessments

Relationship to Scope of:

- PRO Consortium
- CDER-SEALD

Consortium Goals: FDA Perspective

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- Efficiency for industry/FDA time and resources
- Availability of PRO measures in the public domain
- A more transparent advisory process
- Heightened awareness of good measurement principles
- Better information about treatment benefit for patients and other decision-makers

"Better" Information

- Treatment benefit claims in labeling
  - Provide the information needed for decision-makers (clinicians and their patients) to determine whether to accept the risks of treatment
- Identify optimal outcomes assessments to provide information on how patients feel or function early in product development

Claims in Labeling: "Treatment Benefit"

- Improvement in survival
- Improvement or delayed decrement in signs, symptoms, or functioning
- May be measured as…
  - Comparative efficacy
  - Comparative safety

Outcomes Assessments in Clinical Trials

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- Clinical OAs
  - Survival
  - Patient Reported Outcome (PRO)
  - Observer Reported Outcome (ObsRO)
  - Clinician Reported Outcome (ClinRO)
- Non-clinical OAs
  - Biomarkers

Outcomes Assessments: The Claim Includes the Concept

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- Concept = the thing measured
- Well-defined = the concept, explicitly stated
  - Direct versus indirect: measure separately
    - Identify the concepts that directly reflect disease/condition status
    - Measure impact of the disease/condition with a separate score
  - General concepts need a well-defined conceptual framework of the instrument
- "PRO" is not an outcomes assessment concept
- "QOL" is not a claimable concept

Claims in Labeling: Clinically Meaningful in the Context of Use

- Concept and endpoint are clinically meaningful
- Planned endpoint model is clinically meaningful
  - Primary and key secondaries only
  - No replication of concepts
- Prior experience in the targeted context of use provides reviewers with confidence in clinical trial results

Context of Use

- A comprehensive and clear statement that describes the manner and purpose of use and plans for interpretation of a clinical outcomes assessment (COA)
  - Concept measured
  - Target claim
  - Target population
    - Intrinsic and extrinsic sources of heterogeneity considered
  - Type of treatment
  - Type of trial (endpoint model)

Intrinsic Heterogeneity Includes:

- Genetic attributes
  - Sex
  - Race
  - Genetic diseases
- Pathophysiological conditions
  - Age
  - Organ function
  - Disease

Extrinsic (Environmental) Heterogeneity Includes:

- Culture (SES, occupation, education)
- Language
- Personality (eg, willingness to disclose, attention to detail)
- Medical practice norms
- Disease definition
- Therapeutic approach
- Concurrent meds
- Clinical trials/GCP/regulatory environment
- Data collection format
- Instrument format and content

Claims in Labeling: Substantial Evidence

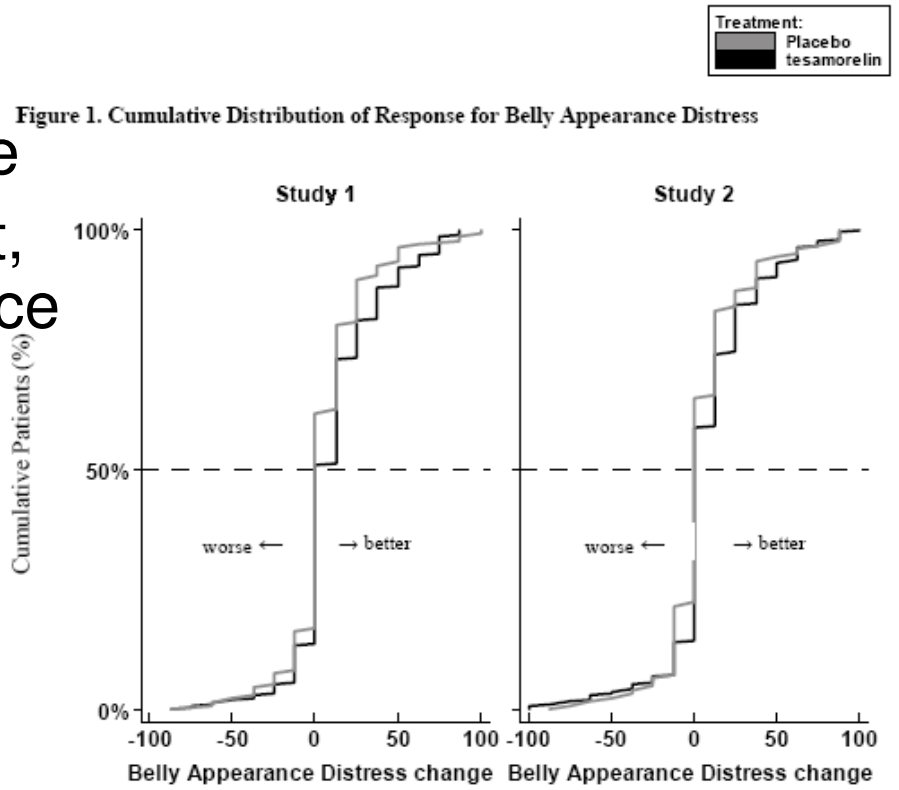
- Adequate and well-controlled studies
  - 21 CFR 314.126 (b)(6) "well-defined and reliable method of assessment of subjects' response"
    - Reviewed according to the specific context of use defined by the investigation
    - A single instrument may be "well-defined and reliable" for multiple contexts of use
    - Each context of use is reviewed separately

- Independent substantiation of experimental results.
  - *Guidance for Industry—Providing Clinical Evidence of Effectiveness for Human Drug and biological Products*

    http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf

Egrifta (tesamorelin)2010

- Indication: reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.
- Endpoints:
  - Visceral Adipose Tissue
  - IGF-I, IGFBP-3, Weight, and Waist Circumference
  - 9-point rating scale of degree of distress associated with belly appearance



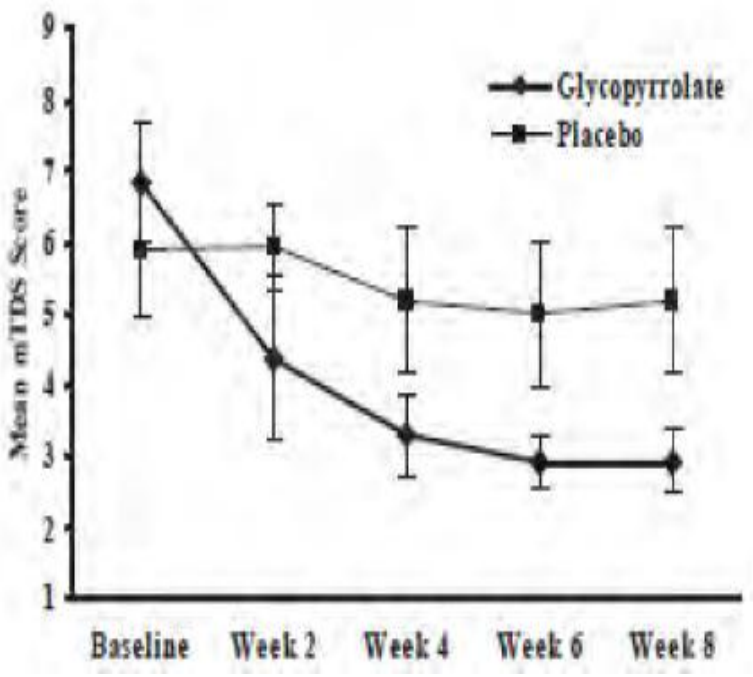
Samsca (tolvaptan) 2009

- Indication: clinically significant hypervolemic and euvolemic hyponatremia

- Important Limitations
  - It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients.

Cuvposa (glycopyrrolate) 2010

- Indication: chronic severe drooling in patients aged 3-16 with neurologic conditions
- Endpoints:
  - 9-point modified Teacher's Drooling Scale (mTDS)
  - Completed 3 times daily by parents/caregivers
  - Responder = subjects with at least a 3-point reduction in mean daily mTDS scores from baseline to Week 8.



Cayston (aztreonam) 2010

- Indication: improve respiratory symptoms in cystic fibrosis (CF) patients with Pseudomonas aeruginosa

- Endpoints:
  - Pulmonary function (FEV1)
  - Changes in respiratory symptoms: patients reported symptoms like cough, wheezing, and sputum production.

Claims NOT in Labeling: WHY NOT???

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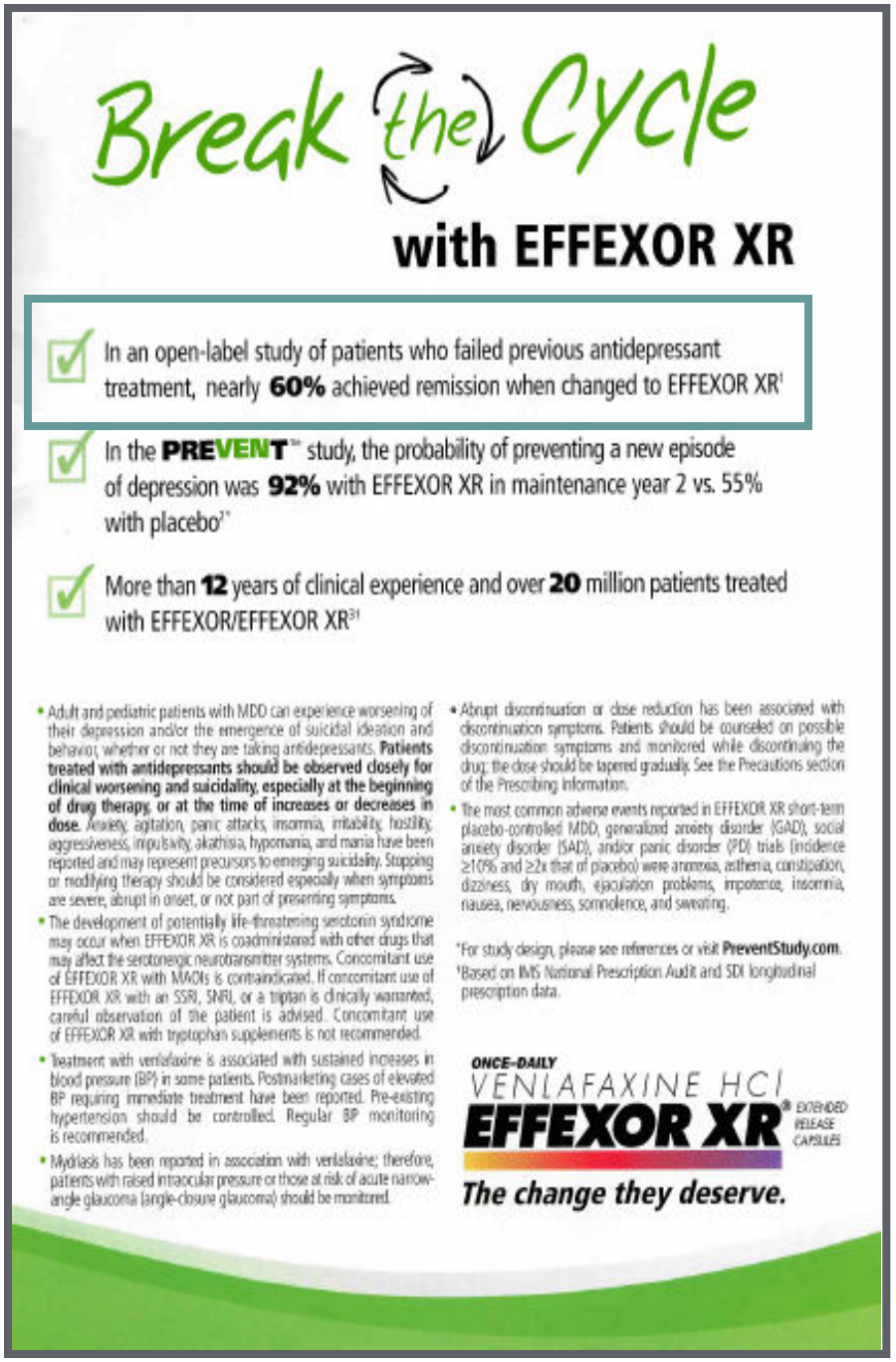
- Desired claim not supported by the assessment
- Claim based on exploratory (ie, secondary, tertiary) endpoints
- Economic claims
- Post-hoc subgroup analyses
- Meta-analyses
- Open-label studies with PROs
- Comparative study issues



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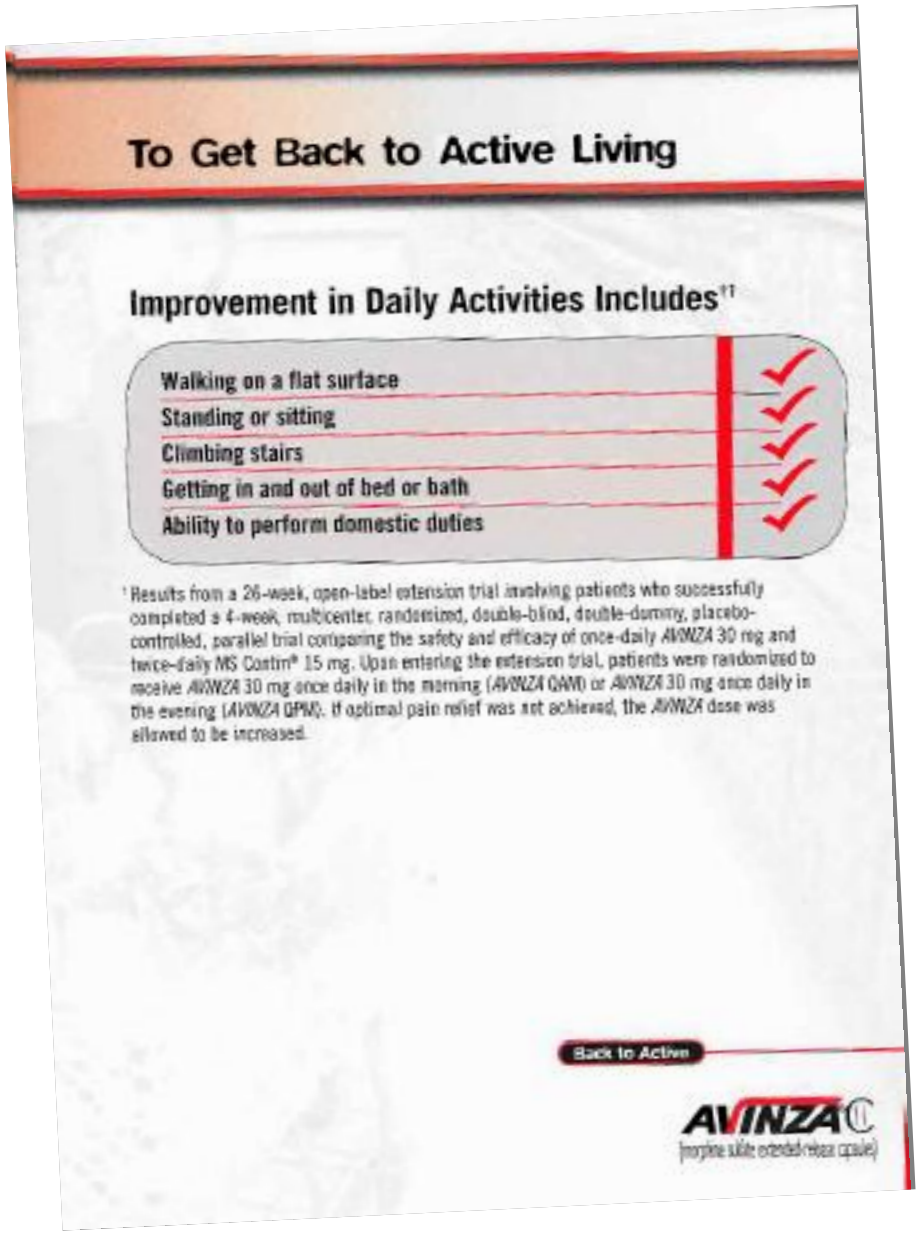
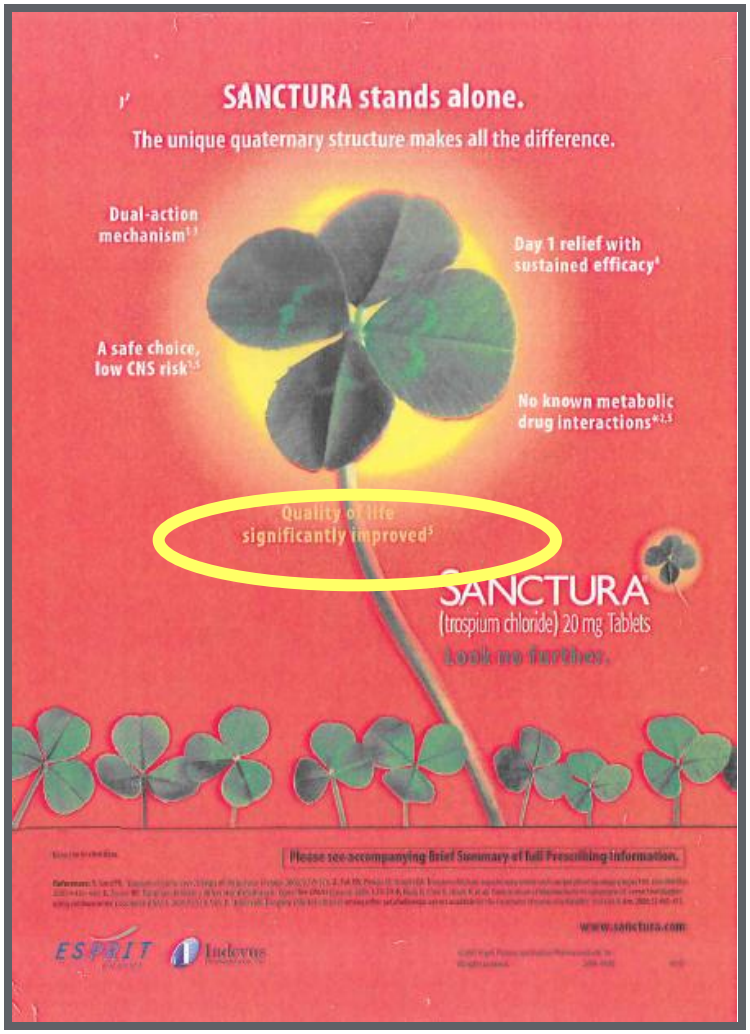
- An open-label study is not an appropriate design to evaluate subjective endpoints (e.g., HAM-D) because it fails to minimize potential bias.
- Biases can result from differences in management, treatment, or assessment of patients, or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment.



- The presentation implies that Avinza can improve patients' function for the individual items of the WOMAC listed
- To FDA's knowledge, individual items of the WOMAC have not been developed to such use

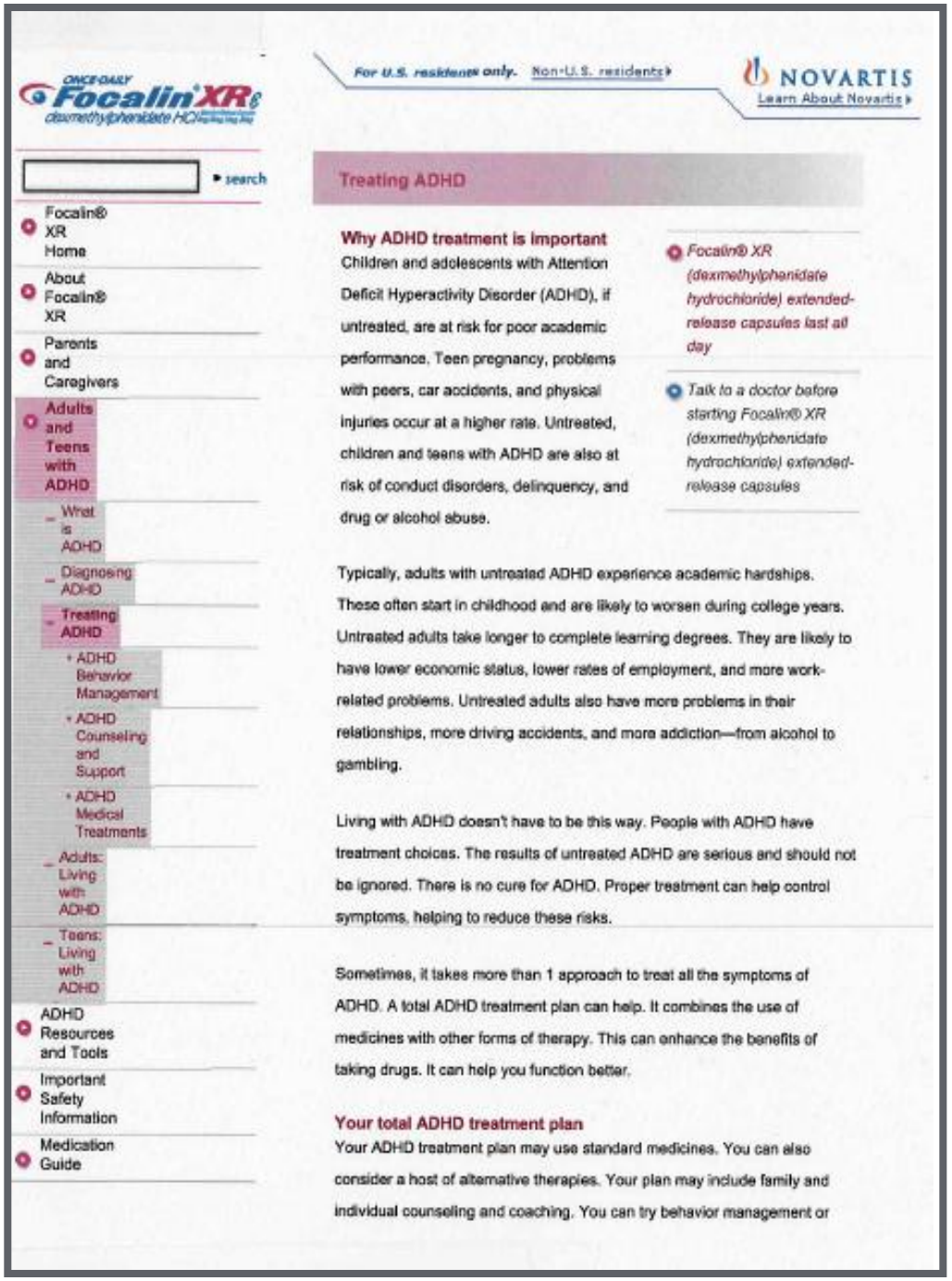
Sanctura (trospium)



- Endpoints supporting the approval: urinary frequency, urge incontinence, urinary volume
- Warning Letter (2009):
  - The claim "Quality of life significantly improved" is misleading
  - Referenced study includes results from the IIQ instrument (impact of OAB on travel, physical activity, social relationships, and emotional health – but not overall "quality of life")

Metozolov ODT (metoclopramide hydrochloride)

- Warning Letter (2010):
  - The totality of this presentation implies that Metozolv ODT offers a therapeutic advantage (i.e., compliance and preference) over other available treatment options
  - The referenced data did not include studies that measured compliance or preference endpoints for Metozolv ODT (another ODT drug was used)



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  - Teens: Living with ADHD
- ADHD Resources and Tools
- Important Safety Information
- Medication Guide

Treating ADHD

Why ADHD treatment is important

Children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD), if untreated, are at risk for poor academic performance. Teen pregnancy, problems with peers, car accidents, and physical injuries occur at a higher rate. Untreated, children and teens with ADHD are also at risk of conduct disorders, delinquency, and drug or alcohol abuse.

- *Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules last all day*
- *Talk to a doctor before starting Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules*

Typically, adults with untreated ADHD experience academic hardships. These often start in childhood and are likely to worsen during college years. Untreated adults take longer to complete learning degrees. They are likely to have lower economic status, lower rates of employment, and more work-related problems. Untreated adults also have more problems in their relationships, more driving accidents, and more addiction—from alcohol to gambling.

Living with ADHD doesn't have to be this way. People with ADHD have treatment choices. The results of untreated ADHD are serious and should not be ignored. There is no cure for ADHD. Proper treatment can help control symptoms, helping to reduce these risks.

Sometimes, it takes more than 1 approach to treat all the symptoms of ADHD. A total ADHD treatment plan can help. It combines the use of medicines with other forms of therapy. This can enhance the benefits of taking drugs. It can help you function better.

Your total ADHD treatment plan

Your ADHD treatment plan may use standard medicines. You can also consider a host of alternative therapies. Your plan may include family and individual counseling and coaching. You can try behavior management or

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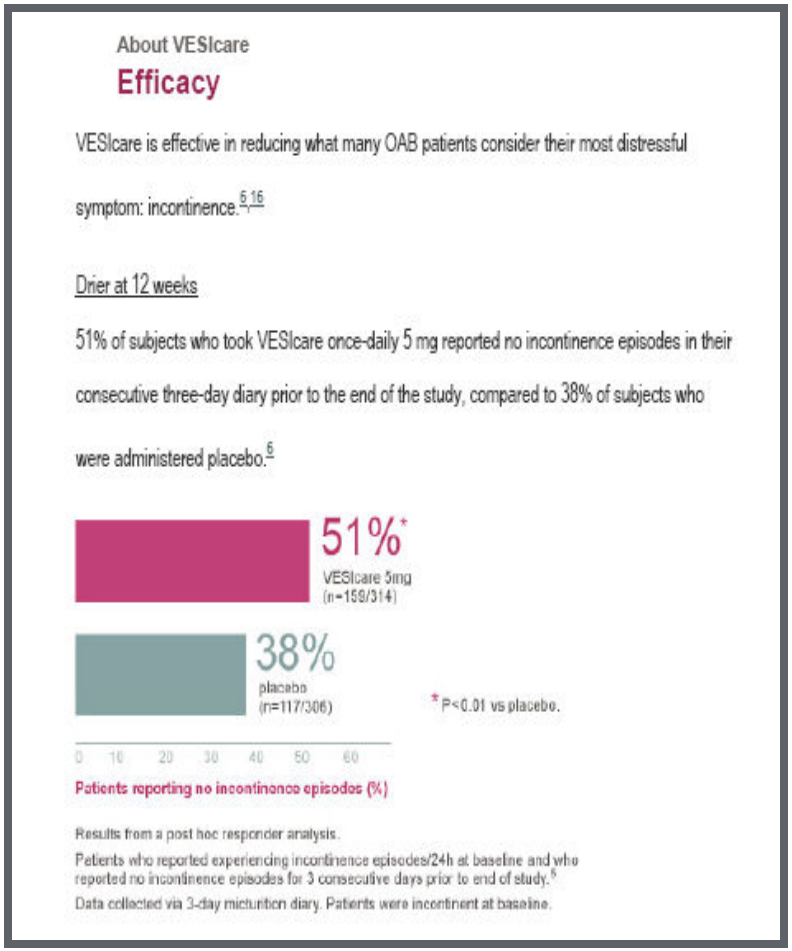
- The claims in the context of the promotional piece imply that Focalin XR may reduce the likelihood or severity of the consequences of untreated ADHD.
- While Focalin XR is indicated for the treatment of ADHD, FDA is not aware of substantial evidence demonstrating that the drug can help patients avoid the listed consequences of ADHD.



- This presentation implies that compared with placebo, a greater percentage of patients treated with VESIcare had no incontinence episodes.
- Data referenced is a post-hoc subgroup responder analysis of data pooled from secondary endpoints.
- No prospectively defined endpoint with a pre-specified statistical analysis plan (SAP).
- Incontinence was not a requirement for study eligibility.
- This study does not support these efficacy claims.

Next Steps to Provide Better Information for Decision-Makers

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- Plan ahead
- Identify the targeted context of use
- Identify, improve or create the OA tools
- Integrate OA plan into the clinical development program
  - Independent protocol development initiatives are rarely successful
  - Must be integrated at the earliest opportunity with the primary study objectives

A Classification Framework for Outcome Assessments

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- Terminology to classify COAs
- Classification based on key characteristics of the assessments
  - Distinguishing Dimensions
  - Focused on characteristics most related to the kind of evidence needed to support Qualification
- Classification useful to guide thinking and studies to evaluate and prove value of a COA

Identification of an Assessment

- Tool-name *for* Stated-concept
  - Includes full description of composition of tool and how measurement is obtained
- Stated-concept identifies the aspect of patient daily (typical) life that is the objective for treatment benefit
  - How the patient feels or functions in typical daily life

Dimensions of an Assessment

- Objectiveness
  - Clinical Measures: an important element not fully objective
  - Biomarkers: ‘fully’ objective
- Who Measures
  - Clinical Measures
    - Patient
    - Clinician
    - Observer

Dimensions of an Assessment

- Relationship to Tangible Clinical Benefit
  - The aspect of typical daily life of intended interest
  - Direct
  - Indirect
- Setting of measurement
  - Nature of patient actions
  - Naturalistic
  - Artificial procedure

Classification of Assessments

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- Clinical vs Biomarker
- Patient vs Clinician vs Observer (vs Instrument)
- Direct vs Indirect
- Naturalistic vs Artificial procedure

Overall Framework

Dimension								
Objectiveness		Clinical Measure (Some Non-objective element Involved)						Biomarker
Who measures		Patient		Clinician		Observer		Instrument
Relationship to Tangible Clinical Benefit		Direct	Indirect	Direct	Indirect	Direct	Indirect	Indirect
How obtained	Naturalistic	VAS *for pain intensity*;	Diary of rescue pain medication use *for pain intensity or frequency*	PANSS *for schizo-phrenia symptoms*	Limb spasticity in MS or stroke *for limb function*;	Obser-vation of seizures *for epilepsy outcomes*	Observation of infant behavior *for distress*	HbA1c *for cardio-vascular outcomes*;
	Artificial Procedure	**NONE Possible**	None identified but possible	**NONE Possible**	9HolePeg (upper limb dexterity) *for upper limb function*	**NONE Possible**	None identified but possible	endocrine stimulation tests *for endocrine organ function)*

Organization Scope Relationship

- PRO Consortium
  - Wider than just "PROs"
- CDER Qualification
  - All types of clinical outcome assessments (SEALD)
    - PRO, ClinRO, ObsRO
  - Biomarkers (OTS)