

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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Outcomes and Labeling: Overview



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



- 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

- 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

- 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

- 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

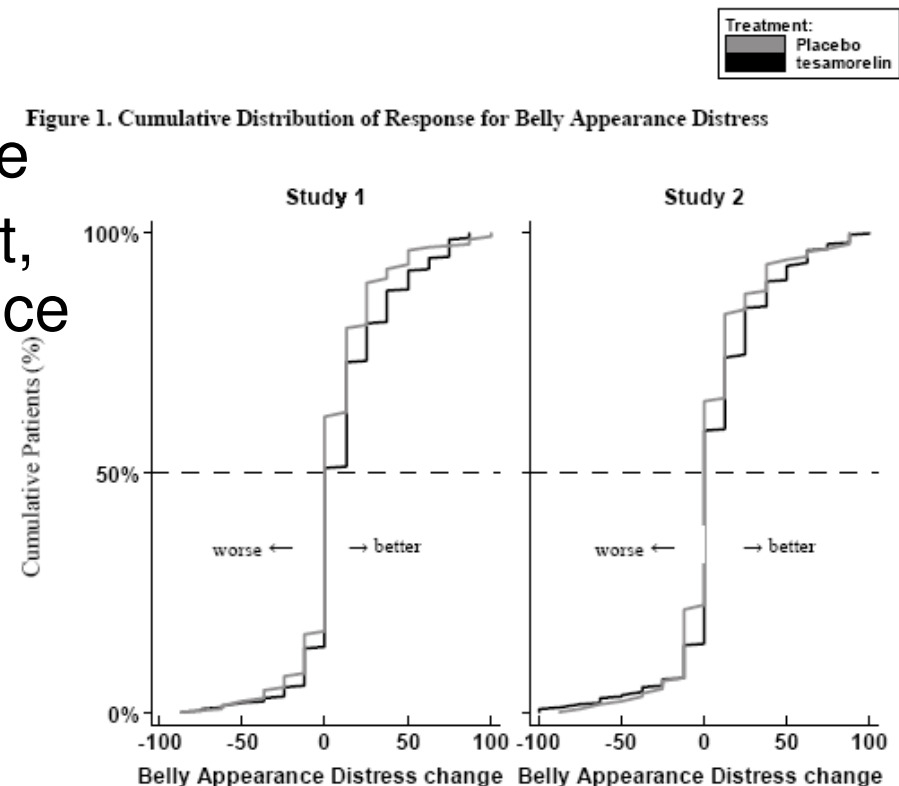
Claims in Labeling: Substantial Evidence

- 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

Figure 1. Cumulative Distribution of Response for Belly Appearance Distress

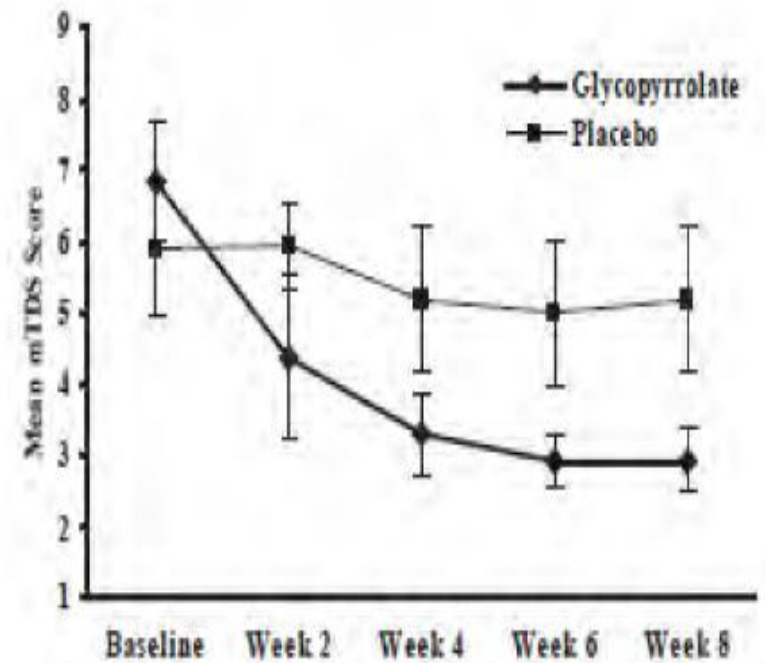


Samsca (tolvaptan) 2009

- Indication: clinically significant hypervolemic and euvoletic 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???

- 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

Break *the* Cycle

with EFFEXOR XR

- ✓ In an open-label study of patients who failed previous antidepressant treatment, nearly **60%** achieved remission when changed to EFFEXOR XR¹
- ✓ In the **PREVENT™** study, the probability of preventing a new episode of depression was **92%** with EFFEXOR XR in maintenance year 2 vs. 55% with placebo²
- ✓ More than **12** years of clinical experience and over **20** million patients treated with EFFEXOR/EFFEXOR XR^{3†}

• Adult and pediatric patients with MDD can experience worsening of their depression and/or the emergence of suicidal ideation and behavior, whether or not they are taking antidepressants. **Patients treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.

• The development of potentially life-threatening serotonin syndrome may occur when EFFEXOR XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems. Concomitant use of EFFEXOR XR with MAOIs is contraindicated. If concomitant use of EFFEXOR XR with an SSRI, SNRI, or a triptan is clinically warranted, careful observation of the patient is advised. Concomitant use of EFFEXOR XR with tryptophan supplements is not recommended.

• Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.

• Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.

• Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.

• The most common adverse events reported in EFFEXOR XR short-term placebo-controlled MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence $\geq 10\%$ and $\geq 2\times$ that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

¹For study design, please see references or visit PreventStudy.com.

²Based on IMS National Prescription Audit and SDI longitudinal prescription data.

ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR®
EXTENDED-RELEASE CAPSULES

The change they deserve.



- 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.

To Get Back to Active Living

Improvement in Daily Activities Includes^{††}

| | |
|------------------------------------|---|
| Walking on a flat surface | ✓ |
| Standing or sitting | ✓ |
| Climbing stairs | ✓ |
| Getting in and out of bed or bath | ✓ |
| Ability to perform domestic duties | ✓ |

^{††} Results from a 26-week, open-label extension trial involving patients who successfully completed a 4-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel trial comparing the safety and efficacy of once-daily AVINZA 30 mg and twice-daily MS Contin® 15 mg. Upon entering the extension trial, patients were randomized to receive AVINZA 30 mg once daily in the morning (AVINZA QAM) or AVINZA 30 mg once daily in the evening (AVINZA QPM). If optimal pain relief was not achieved, the AVINZA dose was allowed to be increased.

Back to Active

AVINZA
(morphine sulfate extended-release capsule)

- 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)

SANCTURA stands alone.

The unique quaternary structure makes all the difference.

Dual-action mechanism^{1,2}

Day 1 relief with sustained efficacy³

A safe choice, low CNS risk^{1,2}

No known metabolic drug interactions^{4,5}

Quality of life significantly improved⁵

SANCTURA
(trospium chloride) 20 mg Tablets
Look no further.

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- 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”)

Metozolv ODT (metoclopramide hydrochloride)

Patients prefer an orally disintegrating tablet (ODT)¹⁻¹⁰

CONVENIENCE **91%** of patients said that the use of orally disintegrating tablets was **convenient or very convenient**¹¹

COMPLIANCE **42%** of patients favored the ease of compliance of orally disintegrating tablets versus 7% who favored conventional tablets¹¹

PREFERENCE **75%** of patients who have difficulty swallowing preferred orally disintegrating tablets to conventional tablets¹⁴

METOZOLV ODT features Zydys® technology

75% of subjects expressed a preference for the orally disintegrating Zydys® formulation compared with a conventional tablet⁹

Metozolv ODT
(metoclopramide HCl)
Orally Disintegrating Tablets
Convenient relief.

¹In a multicenter, observational, cross-sectional study of 724 men and women aged 18 years or older with long-term daily disintegrating tablets. In a real-world, open-label, sequential study of 60 men and women aged 18 years or older who received immediate-release tablets, patients were asked if the tablets "made it more convenient to comply with dosing schedule."¹

⁹A randomized, single-group, crossover study of 36 men and women aged 21 years or older with long-term daily disintegrating tablets. Zydys is a trademark of Solvay Pharmaceuticals.

¹⁴In a randomized, single-blind trial of 150 adult men and women (aged 21 to 80 years) with immediate-release tablets.

Zydys is a registered trademark of Catalent Pharma Solutions.

In clinical studies, the most frequently reported adverse events (≥2% occurrence) were headache, nausea, fatigue, somnolence, and vomiting.

Please see accompanying full Prescribing Information for METOZOLV ODT, including **BOXED WARNING**.

- 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)

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
(dextromethylphenidate hydrochloride) extended-release capsules last all day

Talk to a doctor before starting Focalin[®] XR
(dextromethylphenidate 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

- 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.

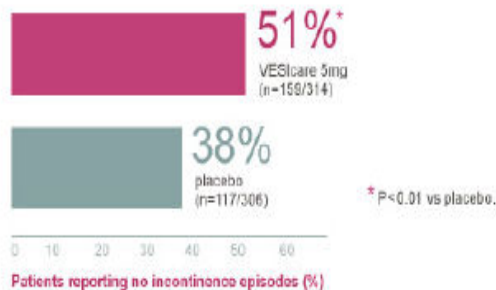
About VESIcare

Efficacy

VESIcare is effective in reducing what many OAB patients consider their most distressful symptom: incontinence.^{6,16}

Drier at 12 weeks

51% of subjects who took VESIcare once-daily 5 mg reported no incontinence episodes in their consecutive three-day diary prior to the end of the study, compared to 38% of subjects who were administered placebo.⁶



Results from a post hoc responder analysis.

Patients who reported experiencing incontinence episodes/24h at baseline and who reported no incontinence episodes for 3 consecutive days prior to end of study.⁶

Data collected via 3-day micturition diary. Patients were incontinent at baseline.

- 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

- 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

- 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

- 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 | <i>VAS for pain intensity;</i> | <i>Diary of rescue pain medication use for pain intensity or frequency</i> | <i>PANSS for schizophrenia symptoms</i> | <i>Limb spasticity in MS or stroke for limb function;</i> | <i>Observation of seizures for epilepsy outcomes</i> | <i>Observation of infant behavior for distress</i> | <i>HbA1c for cardiovascular outcomes;</i> |
| | 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)