Unlocking the Potential Value For Your Business: Building Partnerships Through Understanding Promotional Review

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Executive Director, Global Medical Promotional Review
RALCOY®
ralutinz hcl capsules
Print Ads

“GOALS”

RALCOY is a prescription medication to improve glycemic control with diet and exercise in adults with type 2 diabetes.

YOU HAVE A1C GOALS. RALCOY CAN HELP YOU MEET THEM.

- Once-daily capsule
- Lowers A1C with diet and exercise
- While RALCOY is not for weight loss, some patients may lose weight *

IMPORTANT SAFETY INFORMATION
- RALCOY (ralutinz hcl) capsules has a BOXED WARNING for significant loss in bone mineral density that may be greater with increased duration of use and may not be completely reversible. Bone mineral density testing must occur before starting RALCOY and every 3 months while taking RALCOY.
- Seek medical attention if you experience skin rash or bone fracture as they may be life-threatening side effects of RALCOY.
- RALCOY can cause dizziness, low blood sugar, abdominal pain, and other common side effects. RALCOY should not be used in patients with severe kidney disease.

PLEASE SEE BRIEF SUMMARY BELOW FOR MORE INFORMATION

BRIEF SUMMARY

What is RALCOY used for?
- The use of RALCOY is not limited to patients who have type 2 diabetes.

BRIEF SUMMARY (CONTINUED)

DO NOT USE RALCOY E:
- You are taking a medication that affects your blood sugar.

“TARGET”

RALCOY is a prescription medication to improve glycemic control in adults with type 2 diabetes.

LET RALCOY HELP YOU HIT YOUR A1C TARGET.

- Once-daily capsule
- Lowers A1C with diet and exercise
- While RALCOY is not for weight loss, some patients may lose weight *

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BRIEF SUMMARY (CONTINUED)

DO NOT USE RALCOY E:
- You are taking a medication that affects your blood sugar.
Indicated for lowering blood sugar with diet and exercise in patients diagnosed with type 2 diabetes:

- Decreases HA$_{1c}$ by up to 3.5%!
- Ralcoy® does not cause nausea, unlike Veritas®
- Easy to use!
- Lose over 7 pounds!

Conquer your diabetes!
Indicated for lowering blood sugar with diet and exercise in patients diagnosed with type 2 diabetes.

Decrees HA$_{1c}$ by up to 3.5%!

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Conquer your diabetes!

Important Safety Information
<table>
<thead>
<tr>
<th>Hemoglobin A$_1c$ (%) Decrease from Baseline</th>
<th>Subjects (%) (n=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.9</td>
<td>10</td>
</tr>
<tr>
<td>1 - ≤ 1.9</td>
<td>35</td>
</tr>
<tr>
<td>2 - ≤ 2.9</td>
<td>50</td>
</tr>
<tr>
<td>3 - ≤ 3.5</td>
<td>5</td>
</tr>
</tbody>
</table>
Overstatement of Efficacy #1

- Alcon Research, Ltd. – PATADAY (Untitled Letter Issued: 2/5/2013)
  - Patient Education Brochure
  - “Zero itch within minutes and up to 16 hours later with just one drop daily”
  - Only 30-60% of patients experienced complete relief in clinical trials submitted for approval
Indicated for lowering blood sugar with diet and exercise in patients diagnosed with type 2 diabetes

Hemoglobin $A_{1c}$ mean decreases from baseline in Ralcoy vs Placebo after 30 week study*

<table>
<thead>
<tr>
<th>Hemoglobin $A_{1c}$ (%) Decrease from Baseline</th>
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*All patients were on diet and exercise program

- Ralcoy® does not cause nausea, unlike Veritas®
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Conquer your diabetes!
Overstatement of Efficacy #2

Watson, Inc. – GELNIQUE
(Untitled Letter Issued: 11/30/2010)

- Restroom stall cling at conference
- “Significant reduction in incontinence episodes (P<0.0001) 71%”
  - Footnote: “Represents median change from baseline. Reduction with placebo was 55.6%”
  - In pivotal trials: GELNIQUE episode reduction was 2.7 per day Vs Placebo reduction was 2.0 per day -- a difference of <1 episode reduction per day
- P-value exaggerates significance
- Overstates magnitude of efficacy by omitting material facts

NOTE: \( P \leq 0.05 \) is considered conventional level of statistical significance

FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)
“After getting my glucose under control with RALCOY® and diet and exercise, I’m back at the top of my tennis game!”

- David, Type 2 diabetes patient

Easy to use!

Lose over 7 pounds!

Conquer your diabetes!
Overstatement of Efficacy

- Abbott Laboratories – KALETRA (Warning Letter Issued: 7/14/2009)
  - Patient testimonial of Magic Johnson
  - “It enables me to also be a businessman once I manage my HIV…. I still work and have a long day in the office…”
  - “You’re going to have the same good times…. It’s a normal life… nothing really changes other than you’re taking medicine…”
  - While this may be accurate for Magic Johnson’s own experience, no data supports disease control and preservation of activities of daily living during treatment for typical patients
Misleading Claims about Efficacy

- Pfizer, Inc.– ESTRING
  (Untitled Letter Issued: 6/19/2018)
  - Video of interview featuring physician and patient
    - Both paid and trained spokespersons
  - Patient:
    “...Once we came up with the plan and I began using the product it was pretty much an instant relief.”
    - While this may be accurate for the patient’s experience, no data supports instant relief since endpoints were evaluated at 12 weeks
Indicated for lowering blood sugar with diet and exercise in patients diagnosed with type 2 diabetes

**Hemoglobin A1c mean decreases from baseline in Ralcoy vs Placebo after 30 week study**

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**Easy to use!**

**Lose over 7 pounds!**

**Conquer your diabetes!**
Comparative Claims

- 21 CFR 214.126 Adequate and well-controlled studies
  - Substantial evidence is needed to support a claim
  - Cannot compare clinical trial data from two separate studies and make a conclusion

- Final Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling – Questions and Answers (June 2018)
  - Comparative safety or efficacy information for approved indications that are not included in the label is permissible, HOWEVER...
  - Requires adequate and well-controlled studies such as a **head-to-head study** within the same indication

**NOTE:**
Communications **Consistent with Final Label (CFL)** can present data and information for approved indications that are not included in the label, but must not change safety/risk profile of product
Unsubstantiated Superiority Claims

- Mission Pharmacal – TINDAMAX
  (Untitled Letter Issued: 1/23/2014)
  - Sales sheet
  - “TINDAMAX (tinidazole tablets) is the one and only treatment for BV that gives your patients... better tolerability – than metronidazole... shorter dosing... vs 7-day metronidazole”
    - References cited to support claims were from studies in incorrect patient population and doses
  - Must be supported by head-to-head clinical trials
Indicated for lowering blood sugar with diet and exercise in patients diagnosed with type 2 diabetes

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- Ralcoy® does not cause nausea, unlike Veritas®
- Easy to use!
- Loser over 7 pounds!

Important Safety Information
Inadequate Communication of Indication

- Spriaso, LLC – TUXARIN ER tablets (Warning Letter Issued: 12/13/2016)
  - Product webpage
  - Label states it is not to be used in patients under 18 years of age
  - Not communicated on webpage
  - Does not communicate the full indication of drug
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- **Ralcoy® does not cause nausea, unlike Veritas®**
- **Easy to use!**
- **Lose over 7 pounds!**
RALCOY® can significantly decrease the bone mineral density in patients, which can result in an increased rate of bone fractures. Bone loss is greater with increasing duration of use and may not be completely reversible.

Other side effects of RALCOY® include blurred vision, dry mouth, drowsiness, dizziness, abdominal pain, weakness, and low blood sugar.
Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion (May 2009)

- Risk is inconspicuous compared to benefits
  - Small font size, not bolded
- Risk information should be comparably noticeable and accessible to audiences in terms of language, formatting, and location
  - Must appear with or near benefits as an integral part of the piece and not only through a brief summary page
- Most serious risks are generally material to any presentation of efficacy
Minimization of Risk Information

- Bracco Diagnostics, Inc. – ISOVUE inj. (Untitled Letter Issued: 1/7/2010)
  - Product webpage
  - Incomplete safety information
  - “Please click on the ‘downloads and PI’ tab for full prescribing information”
  - This statement does not mitigate the omission of certain risks and fails to present risk information with comparable prominence to benefits
**Indicated for lowering blood sugar with diet and exercise in patients diagnosed with type 2 diabetes**

**Hemoglobin A1c** mean decreases from baseline in Ralcoy vs Placebo after 30 week study*

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**Easy to use!**

**Lose over 7 pounds!**
False or Misleading Benefit Presentation

- United-Guardian Inc – RENACIDIN (Warning Letter Issued: 12/13/2016)
  - Professional e-mail
  - “Simplifies long-term care”
    - “Easy 30mL dosing and delivery”
      - No references cited to support the product convenience
      - Omits material information from the PI regarding dosage and administration
Convenience Data

- Final Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling – Questions and Answers (June 2018)
  - **Product convenience** information is permissible if presented with substantial evidence in a truthful, non-misleading way
    - Requires close collaboration with clinical development to design appropriate study
  - Other information, such as long-term safety/efficacy data and patient-reported outcomes, could be considered consistent with the label
    - *See additional slides in appendix*
Indicated for lowering blood sugar with diet and exercise in patients diagnosed with type 2 diabetes

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Easy to use!

Lose over 7 pounds!
Clinical Trial Information

End points and assessments

The primary efficacy end point was change from baseline in A1C at week 30 in the main patient cohort. Secondary efficacy measures included change from baseline at week 30 in body weight and FPG. Safety assessments included vital signs, lab measurements, and adverse events as observed or reported.

Statistical analysis

Analyses of change from baseline in A1C, FPG, and body weight were performed by ANCOVA with the treatment group as effect and baseline value as covariate. Point estimates and 95% CI were calculated for the mean change from baseline between treatment groups. Per study design, no P-values were generated for end points in exploratory cohorts.

Table 2: Results at Week 30 in a Placebo-Controlled Study of Ralcoy vs Placebo

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<th>Efficacy Parameter</th>
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<tr>
<td>Body Weight (kg) Change from Baseline</td>
<td>-3.4</td>
<td>-1.8</td>
<td>P &lt; 0.08</td>
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<tr>
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**NOTE:** P ≤ 0.05 is considered conventional level of statistical significance.

FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)
Omission of Material Fact

- Spectrum Pharmaceuticals, Inc.– ZEVALIN (Warning Letter Issued: 7/23/2013)
  - Sales aid for Zevalin
  - “ZEVALIN patients experienced a median time to [cancer] progression of 12.1 months vs 10.1 months for rituximab patients”
    - HOWEVER, label says, “Time-to-disease-progression was not significantly different between study arms”
  - Omitting statistical significance makes a misleading efficacy claim
Communicating Other Endpoints

- Final Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling – Questions and Answers (June 2018)
  - Communications that are consistent with the label can include information that does not necessarily meet the evidentiary standard required for approval or clearance
  - Can present descriptive analyses of individual components of a composite endpoint, without p-values and without additional claims based on these components
  - Cannot use inadequately powered or post-hoc analysis data to support efficacy conclusions either directly (e.g., efficacy claims) or indirectly (e.g., presenting p-values to imply statistical significance)
Indicated for lowering blood sugar with diet and exercise in patients diagnosed with type 2 diabetes

- Ralcoy® does not cause nausea, unlike Veritas®
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Hemoglobin A1c mean decreases from baseline in Ralcoy vs Placebo after 30 week study*

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- Ralcoy® does not cause nausea, unlike Veritas®
- Easy to use!
- Supports weight loss!

Conquer your diabetes!
“RALCOY® is a medication I use to decrease the blood sugar in my patients, and in turn may help prevent potential cardiovascular disease, kidney damage, and cataracts or blindness.”

“I especially like to use RALCOY® if my patient’s blood sugar is uncontrolled. I have noticed my patients seem to feel better as they take this medication.”

- RALCOY® can significantly decrease the bone mineral density in patients, which can result in an increased rate of bone fractures. Bone loss is greater with increasing duration of use and may not be completely reversible.
- Other side effects of RALCOY® include blurred vision, dry mouth, drowsiness, dizziness, abdominal pain, weakness, and low blood sugar.
Post Hoc Analysis

- Guidance for Industry: Multiple Endpoints in Clinical Trials (January 2017)
  - Post hoc analyses of trials can be used to generate hypotheses for future testing, but they do not yield definitive results
  - Biased analysis and results influenced by desire for trial success
  - No credible way to correct for multiplicity of statistical analyses or control Type I error rate
  - Post hoc analyses on their own cannot establish effectiveness
Misleading Risk Presentation

- Pfizer, Inc.– ESTRING (Untitled Letter Issued: 6/19/2018)
  - DTC video of interview featuring physician and patient
  - Patient: “I do not experience any side effects. I’m, for me, I was able to just feel relief.”
  - Misleadingly suggests that typical patient will not experience side effects
  - Additionally, video fails to disclose any safety information
Delivery of Risk Information

- Guidance for Industry: Consumer-Directed Broadcast Advertisements (August 1999)
  - “Advertisements broadcast through media such as television, radio, or telephone communications systems must disclose the product’s major risks in either the audio or audio and visual parts of the presentation.”
Risk Information in Media Ads

- Celgene Corporation – OTEZLA
  (Warning Letter Issued: 12/12/2016)
  - TV advertisements
  - Song is played loudly during the risk information statement

- Supernus Pharmaceuticals – OXTELLAR ER
  (Warning Letter Issued: 10/31/2016)
  - Video featuring Key Opinion Leader
  - Physicians states benefits without risk information.
  - Risk information is displayed at end of video, which is not likely to catch viewer’s attention
Misleading Risk Presentation

- Collegium Pharmaceutical, Inc. – XTAMPZA ER capsules (Warning Letter Issued: 2/9/2018)
  - Exhibit booth at 2017 ASHP* Summer Exhibition
  - Risk statements displayed near the floor, often behind table or chair, as observed by OPDP representative at the meetings
  - Safety and risk information displayed in side panel of principal display
    - Small font, no associated visual elements

* ASHP = American Society of Health-System Pharmacists
VP of Marketing is struggling to understand why the Advertising and Promotional Review Committee is requiring so many changes.

What is the risk?
## Corporate Penalties

<table>
<thead>
<tr>
<th>Company</th>
<th>Fine ($)</th>
<th>Reason</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>2.3 Billion</td>
<td>Off-Label Promotion</td>
<td>January 2009</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>1.42 Billion</td>
<td>Off-Label Promotion</td>
<td>January 2009</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>520 Million</td>
<td>Off-Label Promotion</td>
<td>April 2010</td>
</tr>
<tr>
<td>GalaxoSmithKline</td>
<td>3 Billion</td>
<td>Promotion for Unapproved Age</td>
<td>July 2012</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>2.2 Billion</td>
<td>Off-Label Promotion</td>
<td>November 2013</td>
</tr>
<tr>
<td>Endo</td>
<td>192.7 Million</td>
<td>Off-Label Promotion</td>
<td>February 2014</td>
</tr>
</tbody>
</table>
Individual Liability

- *United States v. Park* (1975) – “Park Doctrine”
  - US Supreme Court rules FDA can seek conviction against responsible corporate officers (RCO) for corporate misdemeanors
  - **Anyone with authority to prevent or detect and correct violation** is a responsible corporate officer

  - FDA outlines criteria and intentions for referral to Department of Justice for prosecution under Park Doctrine

  - Department of Justice approach to seek **individual accountability** in corporate misconduct
Criminal and Civil Charges: Wire Fraud

- **SURVIVAL BENEFIT**
  - Reduces Mortality by 70% in Patients with Mild to Moderate Disease
  - In the overall population:
    - 40% decrease in mortality in favor of Actimmune vs. placebo ($p = 0.084$)
  - Of the 254 patients with mild to moderate disease...
    - 70% decrease in mortality in favor of Actimmune versus placebo ($p = 0.004$).

- **InterMune Inc. – ACTIMMUNE**
  - CEO wrote headline and approved press release claiming survival benefit data from Phase III clinical trial
  - Primary endpoint: Progression-free survival in patients with IPF vs. placebo
    - $p = 0.084$ in overall population
  - In post-hoc analysis of subpopulation:
    - $p = 0.004$ in mild to moderate IPF

- **United States v. Harkonen (2009)**
  - Court pursues $200,000 fine and 20 years in prison for CEO

* IPF = Idiopathic Pulmonary Fibrosis
# Individual Prosecution

<table>
<thead>
<tr>
<th>Executive</th>
<th>Penalty</th>
<th>Reason</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>CEO (InterMune)</td>
<td>6 months house arrest $20,000</td>
<td>Approval of Press Release of False and Misleading Efficacy Claims</td>
<td>September 2009</td>
</tr>
<tr>
<td>2 Sales Managers (Pfizer)</td>
<td>6 months house arrest 2 years probation $75,000</td>
<td>Off-label Promotion</td>
<td>December 2009</td>
</tr>
<tr>
<td>Lawyer Medical Director President (Purdue Pharma)</td>
<td>$34.5 Million Total ($600 M Corporate Fine)</td>
<td>Understating Risk Information</td>
<td>May 2007</td>
</tr>
</tbody>
</table>
Appendix

Includes:

Guidance for Industry: Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers (Jun 2018)

Educational Standards of Pharma Communications

Additional Cases of Individual Prosecutions
Consistent with Final Label (CFL)

- Final Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling – Questions and Answers (January 2019)
  - Communicating data and information about approved/cleared uses of products that are not contained in the label but consistent with the final label (CFL)
  - Three factors considered in determining CFL:
    1. Consistent with label in:
      i. Indication
      ii. Patient population
      iii. Limitations and directions for use, handling, or preparing product
      iv. Dosing and administration
    2. Communication’s potential to increase patient risk relative to label
    3. Communication must not represent or suggest conditions under which the directions for use in the label may not allow for the safe and effective use of the product
- Requires scientifically appropriate and statistically sound evidence, including appropriate context information and disclosure of limitations
Consistent with Final Label (CFL) - Continued

Examples provided in FDA Guidance:

**Information that COULD be CFL:**
- Long-term safety/efficacy if approved for chronic use
- Effect or use in patient subgroups within approved population
- Onset or duration of action for approved indication
- Safety/efficacy comparison to another product approved for the same indication
- Additional context about adverse reactions
- Patient-reported outcomes
- Product convenience
- Additional context about mechanism of action

**Information that is **NOT** CFL:**
- Use of product in unapproved disease or condition
- Use of product in unapproved population
- Use of product in an unapproved stage, severity, or manifestation of disease
  - E.g., Mild vs severe asthma
- Use of product as monotherapy when only approved for use in conjunction with other products or therapies
- Use of product through unapproved route of administration, strength, dosage, or regimen
- Use of product in unapproved dosage form
“Pharma ads are sunnier than they used to be. But are they better?” – *FiercePharma* (May 2018)

- Study compared pharmaceutical advertisements in 2016 to those from 2004
- More lacking in health condition and drug education
- More likely to focus only on post-medication mood, health, and social benefits
- Ads fulfill public health function in addition to marketing function

“DTC Broadcast Advertisements for Pharmaceuticals: Off-label Promotion and Adherence to FDA Guidelines” – *Journal of General Internal Medicine* (February 2018)

- Few ads fully compliant to FDA guidelines for DTC advertising
- Data rarely provided, risks are not quantified, suggestive off-label promotion
Criminal and Civil Charges: Off-Label Promotion

- **Pharmacia & Upjohn (Pfizer) – BEXTRA**
  - Bextra gains FDA approval in 2001 for treatment of arthritis and menstrual discomfort
  - Regional manager charged with directing sales team to promote off-label uses of Bextra in the prevention of deep vein thrombosis in joint replacements
  - Sales manager charged with obstruction of justice for instructing sales representatives to delete evidence of off-label communications from computers
Criminal and Civil Charges: Misbranding

- **Purdue Pharma L.P. – OXYCONTIN**
- Warning letter issued in 2003 for print ads in *JAMA*
- Omits safety information regarding formulation
- **United States v. The Purdue Frederick Co., Inc., et. al**
- Guilty plea in 2007
- Sales representatives misled physicians on abuse potential and associated risks, among other charges