Communicating About Black Box Warnings

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The need to provide clear and appropriate guidance to health care professionals in a timely manner about medicines and biologics has never been greater. Product sponsors and regulators continue to take measures to ensure that important general prescribing and dispensing information is clearly and comprehensively presented but also that extraordinary information is called to the attention of practitioners so that they take note and adhere to the information when prescribing the medications. The Food and Drug Administration (FDA) and product developers have several regulatory tools at their disposal to ensure the information gets disseminated. These include restricted distribution systems, patient and health professional registries, directed patient and professional education and outreach, and other evolving techniques under the ever-broadening rubric of Risk Evaluation and Mitigation Strategies (REMS).

One of the oldest and most widely used of these strategies is adding a Black Box Warning to the FDA approved labeling. These information enhancements to the general labeling format are designed to help direct prescriber and dispenser attention not only to an extraordinary risk but also very valuable information providing guidance on the proper use of these useful and often unique treatments. A full discussion of all aspects of Black Box Warnings is beyond the scope of this brief thought piece, so we will focus on what drug and biologic sponsors can do to help guide appropriate use of products with such highlighted warnings.

Products with Black Box Warnings often provide important therapeutic benefits. In this day and age, issuance of such a labeling requirement need not condemn such therapies to a Forbidden Drug List. Unfortunately, all too often Black Box Warnings are viewed by prescribers and formulary decision makers as absolute contradictions to the use of such products or to put unreasonable impediments to access. This often denies or inappropriately delays patient access to valuable drugs or biologics. Equally unfortunately, product sponsors view a Black Box Warning as a reason to not put resources to the product clinical adoption.

The dual inform-and-advice purpose of Black Box Warnings is clearly seen in the following abstract from the FDA website¹ (emphasis added):

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¹ FDA website
A boxed warning is ordinarily used to highlight one of the following situations for prescribers:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug that it be considered in assessing the risks and benefits of using the drug

or

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring of certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)

or

- FDA approved the drug with restrictions to ensure safe use because FDA has determined that the drug can be safely used only if distribution or use is restricted.

As highlighted in the above excerpt from the FDA’s industry guidance, and contrary to popular perspective by providers and some formulary managers, this highlighted set of side effects exists not to stop access for patients who need treatment, but to provide highlighted guidance and call to attention specific information on how to use these medications safely. When it is advisable, or required, to include a Black Box Warning product innovators and product sponsors have an important obligation— and an opportunity—to meet with prescribers, formulary influentials and dispensers to inform them not only of the nature of the warning but also how to appropriately manage them, to provide access to needed treatments safely, and in correctly selected patients.

The amount, complexity and clinical context that needs to be conveyed regarding Black Box Warning products, or products with other types of REMS requirements, is usually beyond the scope of expertise of general pharmaceutical company professional representatives. Pharmaceutical companies have, in part, begun to utilize health professional personnel (such as Pharmacists) to engage prescribers in the needed dialogue about these drugs and biologics. It is equally important to provide formulary managers, health system professionals and other local and regional distribution managers and pharmacists with programmatic support to properly support practitioners and patients. This process, particularly in the initial stages of a new Black Box Warning for an existing product, is a daunting and resource intensive process until the procedures and information are institutionalized. In addition, particularly when a Black Box Warning is issued or is removed, from an existing drug or biologic, properly informing patients, caregivers and other non-health professional stakeholders is essential to insuring appropriate continuity of care. Pharmacists are in a unique position to not only be able to address the clinical information and guidance but also in policy and procedure, distribution and patient counseling/instruction.

Organizations such as Pharmacist Partners provide resources to help meet the outreach, informational and clinical needs of clinicians, health organizations and patients for Black Box or REMS situations. Developing customized, rapidly deployable and focused skills in an advisory,
consulting or a finite field based initiative can be particularly important in resource constrained situations or when a time-defined program needs to be put into place.

**Recent Black Box warnings include**:
- Ariad’s Inclusig®: December 2013
- Pfizer’s Tygacil®: Sept. 2013
- GSK’s Arzerra® and Rituxan®: Sept. 2013

For a full list see Appendix, below.

**APPENDIX:**
As of 02/11/2014, data condensed to just BOXED WARNING information.

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>Date BOXED WARNING Approved by FDA to reflect Safety Labeling Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cozaar (losartan) 25 mg, 50 mg, and 100 mg Tablets</td>
<td>01/2014</td>
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<tr>
<td>Hyzaar (losartan/hydrochlorothiazide) 50/12.5 mg, 100/12.5 mg, and 100/25 mg Tablets</td>
<td>01/2014</td>
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<tr>
<td>Tysabri (natalizumab) Injection</td>
<td>12/2013</td>
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<tr>
<td>Entereg (alvimopan) Capsules</td>
<td>10/2013</td>
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<tr>
<td>Lovenox (enoxaparin sodium) injection</td>
<td>10/2013</td>
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<tr>
<td>Ofirmev (acetaminophen) Injection</td>
<td>10/2013</td>
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<tr>
<td>Modicon (norethindrone/ethinyl estradiol)</td>
<td>10/2013</td>
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<tr>
<td>Ortho-Cept (desogestrel/ethinyl estradiol)</td>
<td>10/2013</td>
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<tr>
<td>Ortho-Cyclen (norgestimate/ethinyl estradiol)</td>
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<tr>
<td>Ortho Novum (norethindrone/ethinyl estradiol)</td>
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<tr>
<td>Ortho Tri-Cyclen (norgestimate/ethinyl estradiol)</td>
<td>10/2013</td>
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<tr>
<td>Arzerra (ofatumumab) Injection</td>
<td>09/2013</td>
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<tr>
<td>CombiPatch (estradiol/norethindrone acetate transdermal system)</td>
<td>09/2013</td>
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<tr>
<td>Potiga (ezogabine) tablets 50 mg, 200 mg, 300 mg, 400 mg</td>
<td>09/2013</td>
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<td>Drug Name</td>
<td>Date</td>
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<tr>
<td>Rituxan (rituximab)</td>
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<tr>
<td>Tasigna (nilotinib) capsules, 150 mg and 200 mg</td>
<td>09/2013</td>
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<tr>
<td>Tygacil (tigecycline) for Injection</td>
<td>09/2013</td>
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<tr>
<td>Xarelto (Rivaroxaban) Tablets</td>
<td>08/2013</td>
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<tr>
<td>Nizoral (ketoconazole) Tablets</td>
<td>07/2013</td>
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<tr>
<td>Depakene (valproic acid) Capsules and Oral Solution</td>
<td>07/2013</td>
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<tr>
<td>Depakote (divalproex sodium) Delayed Release</td>
<td>07/2013</td>
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<tr>
<td>Depakote ER (Extended Release) Tablets</td>
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<tr>
<td>Depakote Sprinkle Capsules (divalproex sodium coated particles in capsules)</td>
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<tr>
<td>Depacon (valproate sodium) Injection</td>
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<tr>
<td>Stavzor (valproic acid) Delayed Release Capsules</td>
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<td>SynalgosDC (dihydrocodeine bitartrate, aspirin and caffeine) Capsules</td>
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<td>Soma Compound with Codeine (carisoprodol, aspirin, and codeine phosphate) Tablets</td>
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<td>Fiorinal with Codeine (butalbital, aspirin, caffeine, and codeine phosphate, USP) Capsules</td>
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<td>Vivelle-Dot (estradiol transdermal system)</td>
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<td>Promethazine and Codeine Syrup</td>
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<tr>
<td>Pradaxa (Dabigatran Etexilate Mesylate) Capsules</td>
<td>04/2013</td>
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Other Sources:
About the author:
Dr. Giorgianni was at Pfizer for 27 years. His last assignment was as the Director External Relations and Editor-In-Chief of The Pfizer Journal. During his tenure there he was engaged in several US and global product launches including for Cefobid, Aricept, Lipitor, Zoloft and Viagra. Dr. Giorgianni was responsible for developing and directing relationships with professional and voluntary health associations and for various image and reputation management projects to support product and research strategies. He is the author or co-author of over 55 peer reviewed and general public articles and presentations on health. Currently, Dr. Giorgianni is Chair of the American Public Health Association's Men’s Health Caucus and an Advisor to Pharmacist Partners. Dr. Giorgianni is President of Griffon Consulting Group Inc., and is a practicing pharmacist.