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What Does the "Gluten Free" Label on Your Food Really Mean?

By: Christopher Boreen, Pharm.D.

Introduction: Patients with celiac disease (CD) will now have a clear definition of what the "gluten-free" label means on their food. Following several years of consideration, the U.S. Food and Drug Administration (FDA) has established clear standards for food manufacturers to make any of the following labeling claims: gluten-free, without gluten, free of gluten, or no gluten.[1]

Image from: http://www.prweb.com/releases/glutenfreesnacks/foodsthatareglutenfree/prweb10716303.htm

Background: Celiac disease, present in 0.6-1% of the population worldwide, is a systemic immune response occurring in the small intestine following the ingestion of gluten, a protein found in various wheat, rye, and barley products.[1,2] This immune response over time produces inflammation, leading to damage to the intestines.[3] This damage can result in poor absorption of nutrients, which is why patients may present with iron deficiency, chronic fatigue, and/or reduced bone mineral density.[2] Other more common symptoms associated with this condition include chronic diarrhea, weight loss, and abdominal distention which are prevalent in 40-50%

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Breo™ Ellipta™ for Chronic Obstructive Pulmonary Disease

By: Sara Wolf, Pharm.D.

Background: Chronic obstructive pulmonary disease (COPD) is characterized by constant airflow limitation and associated with an enhanced chronic inflammatory response in the lungs.[1] The leading risk factor for developing COPD is tobacco smoking. The primary symptoms are chronic cough, chronic sputum production, dyspnea, and wheezing. The clinical diagnosis of COPD is made when the forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio is less than 0.70. The severity or staging of COPD derived from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines is summarized in Table 1. Treatments for COPD depend on the stage of the disease, with short-acting agents used in mild disease and long-acting agents in moderate-to-severe disease.

Breo™ Ellipta™: Breo™ Ellipta™ (fluticasone furoate/vilanterol) is a new once-daily medication for the treatment of moderate-to-severe COPD manufactured by GlaxoSmithKline.[2] It is a combination inhaled corticosteroid (ICS) and long-acting beta agonist (LABA). In May 2013, fluticasone furoate/

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of patients with CD.[1,2] The severity of this condition has been found to be quite variable in clinical presentation, antibody response, and damage to the small intestine.[2] Non-celiac gluten sensitivity is a distinct condition with markedly similar symptomatology as CD, but identification of this condition lacks an objective diagnostic test.[3] Whereas with CD, measurement of serum IgA is typically used for initial screening and diagnosis is confirmed following upper endoscopy.[2] Currently, no cure exists for CD, but a gluten-free diet can help control symptoms.[1,2]

FDA Definition: Food manufacturers may make claims of being either gluten-free, without gluten, free of gluten, or no gluten as long as the food does not contain any of the following:

1. An ingredient that is any type of wheat, rye, barley, or crossbreeds of these grains
2. An ingredient derived from these grains that has not been processed to remove gluten
3. An ingredient derived from these grains that has been processed to remove gluten, if it results in the food containing 20 or more parts per million gluten

Although some food manufacturers may already label their products according to these new guidelines, full compliance is expected by August 5, 2014.[1,4]

What Patients Should Know: Since the new definition will not become a requirement for food manufacturers until August 5, 2014, it is important that patients with CD or gluten sensitivities evaluate the risks and benefits of the foods they consume until all manufacturers are in compliance with the new definition. Patients need to be aware that their medications may also contain gluten, which can be used as an inactive ingredient to hold ingredients of the medication together.[5] Since this new definition only applies to food, it is important that patients with CD or gluten sensitivities ask their pharmacist to verify the presence or absence of gluten prior to taking any prescription medications, over-the-counter products, and dietary supplements. Particular ingredients pharmacists should be aware of that may indicate the presence of gluten include: wheat, modified starch, pregelatinized starch, pregelatinized modified starch, dextrates, dextrin, dextrimaltose, and caramel coloring.[5] The pharmacist can confirm the presence or absence of gluten by calling the manufacturer. Patients should also be aware of changes in drug manufacturers for a particular pharmaceutical product as it is possible that gluten content of the same medication produced by different manufacturers could differ.

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vilanterol (FF/VI) was approved by the Food and Drug Administration (FDA) for the long-term, once-daily, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with COPD. The most common adverse reactions seen in clinical trials were nasopharyngitis, oral candidasis, upper respiratory tract infection, and headache.

Table 1: Severity of COPD*†

Stage 1	Mild	$FEV_1 \geq 80\%$
Stage 2	Moderate	$50\% \leq FEV_1 < 80\%$
Stage 3	Severe	$30\% \leq FEV_1 < 50\%$
Stage 4	Very Severe	$FEV_1 < 30\%$

*FEV_1 is based on the predicted value
†Based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines
COPD=Chronic obstructive pulmonary disease
FEV_1=Forced expiratory volume in 1 second

Pharmacology: Fluticasone furoate is a trifluorinated corticosteroid with a half-life of 24 hours, which makes it distinctly different from fluticasone propionate which has a half-life of about 12 hours.[2] Fluticasone furoate has anti-inflammatory activity, but its exact mechanism of action in treating COPD is unknown. Vilanterol is a long-acting beta agonist with a half-life of 21.3 hours. Like fluticasone furoate, vilanterol has a longer duration of action than other comparable medications such as salmeterol which has a half-life of 5.5 hours. Vilanterol is selective for $beta_2$ receptors, the predominant beta receptor in the bronchial smooth muscle.

Clinical Efficacy: Fluticasone furoate/vilanterol has been evaluated in both lung function and exacerbation trials for efficacy and safety.[3,4] Lung function was evaluated in two 24-week trials, which were randomized, double-blind, and placebo-controlled. The co-primary endpoints in both trials were weighted mean FEV_1 post-dose on day 168 and change in trough FEV_1 on day 169 post-dose. The multiple treatment arms in both trials are listed in Table 2. In both trials it was found that the combination fluticasone furoate/vilanterol had sustained improvement on lung function over the 24-week period. Exacerbations were assessed in two 1-year clinical trials, which were double-blind, parallel-group, and randomized. The primary endpoint of both trials was the annual rate of moderate-to-severe COPD exacerbations. Patients in both trials were randomized to receive one of the following: VI 25 mcg, FF/VI 200/25 mcg, FF/VI 100/25 mcg, or FF/VI 50/25 mcg. In a combined analysis of the two trials, there was found to be statistically fewer moderate-to-severe exacerbations in patients taking any strength of the combination product.[5]

Table 2: Treatment Arms in Lung Function Trials

Trial One	Trial Two
FF/VI 200/25mcg	FF/VI 100/25mcg
FF/VI 100/25mcg	FF/VI 50/25mcg
VI 25mcg	VI 25mcg
FF 200mcg	FF 100mcg
FF 100mcg	Placebo
Placebo	

FF=Fluticasone furoate
VI=Vilanterol

Clinical Application: The fluticasone furoate/vilanterol inhaler has a 24-hour duration making it a once-daily medication. For outpatients, the once-daily dosing can increase compliance as all the other ICS/LABA inhalers require twice-daily dosing. For inpatients, compliance is not an issue so its utility in the hospital setting over the current formulary ICS/LABA medications is limited. Fluticasone furoate/vilanterol is only FDA approved in the 100/25 mcg strength, so dosage adjustments would be difficult to determine.

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Weighing the Risks and Benefits of Medication Use in Lactating Mothers

By: Maya Wai, PharmD

Introduction: Breastfeeding mothers may be advised to stop breastfeeding or even discontinue certain medications to prevent infant exposure to potentially harmful drugs.[1] There are often limited data on drug excretion into breast milk and if there is a clinically significant effect on the infant. In 1983, the American Academy of Pediatrics (AAP) first published a statement on the transfer of drugs into human milk, which has been revised over the years to incorporate new data.[2-5] However, these AAP statements cannot keep pace with new and rapidly changing information. A comprehensive and current database LactMed (http://toxnet.nlm.nih.gov) provides information on drug levels in human milk and infant serum, adverse effects on infants, effects on lactation, and potential alternative therapies.[6] The latest version of AAP's recommendations regarding the transfer of drugs into human breast milk, published in September 2013, highlights select drug classes of interest in the care of the lactating mother.[1]

Drug Selection in Lactating Mothers: Generally, the chemical properties that promote drug excretion into breast milk, include: small molecular weight, high lipophilicity, lack of ionization, low volume of distribution, and low maternal serum protein binding.[1] Drugs with long half-lives are likely to accumulate and drugs with high bioavailability are easily absorbed by the infant. Higher maternal doses, timing of doses, and duration of therapy can affect infant exposure. The age of the infant, underlying medical conditions, reduced clearance or immaturity of metabolic pathways should also be considered. Table 1 lists commonly used drugs and classes with well-defined recommendations for nursing mothers.

Antidepressants, Anxiolytics, and Antipsychotics: Due to a paucity of relevant studies, the long-term effects of psychoactive drugs on the nursing infant are generally unknown.[1] Additionally, interpretation of the adverse effects reported in the biomedical literature could be confounded by prenatal treatments or exposure to multiple therapies. Many psychoactive drugs have <2% excretion in breast milk.; those achieving a clinically significant level (>10%) should be avoided during lactation.

Treatments for Smoking Cessation, Substance Abuse, and Alcohol Dependence: There are limited data on medications used to treat substance abuse, alcohol dependence, or smoking cessation in nursing mothers.[1] The use of some of these drugs may outweigh the risks of continued behaviors. Bupropion and varenicline are not recommended to be used during breastfeeding due to the potential for serious central nervous system (CNS) side effects occurring in the nursing infant. Additionally, disulfiram and naltrexone are not compatible with breastfeeding.

Pain Medications: In general, the lowest dose and shortest duration of pain therapy should be utilized to minimize breast milk excretion, CNS depression, and accumulation in the infant.[1] Acetaminophen toxicity is less common in neonates than older infants because of their immature cytochrome-P450 (CYP) enzymes. Nonsteroidal anti-inflammatory agents (NSAIDs) should be avoided if infants have ductal-dependent cardiac lesions.

Galactagogues and Herbal Products: Agents to stimulate lactation and herbal products have very limited data and are not recommended by the AAP.[1] A lactation specialist should be consulted for non-pharmacologic techniques to increase milk production. Additionally, the use of the recommended daily allowance of iron and vitamins found in prenatal supplements is generally considered safe.

Diagnostic Imaging: Breastfeeding should be interrupted for ≥3 weeks after administration of ^{125}I, ^{22}Na, and ^{67}Ga. Since the lactating breast has a greater affinity for ^{131}I, lactation should be stopped 4 weeks before whole-body procedures with ^{131}I ; this will allow for a lower radiation dose reducing the risk for breast cancer. Breastfeeding should not be continued after this procedure. However, it can be continued after treatment with iodinated contrast or gadolinium.

Vaccines: Breastfeeding does not interfere with the infant's immune response to a vaccine.[1] Inactivated vaccines do not pose a risk to the infant, and the viral components of most live vaccines are not excreted in breast milk. However, smallpox and yellow-fever vaccines are contraindicated in nursing mothers.

Summary: Limited data exist regarding drug excretion into breast milk and if there is a clinically significant effect on the infant. Prescribers must weigh the risks to the nursing infant and the benefits of the drug for the mother. Generally, drugs that have high excretion into the breast milk should be avoided in nursing mothers or be utilized at the lowest dose for the shortest duration. LactMed (http://toxnet.nlm.nih.gov), a comprehensive database, provides current information to patients and prescribers to help make informed decisions about drug therapy during breastfeeding.

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Table 1: General Guidance for Drug Selection in Lactating Mothers[1]

Drug Class	Recommended	Not Recommended
Antidepressants, Anxiolytics, Antipsychotics	Check individual medication recommendations on LactMed (http://toxnet.nlm.nih.gov)	Buproprion Citalopram Clomipramine Diazepam Doxepin Fluoxetine Fluvoxamine Lamotrigine Lithium Mirtazapine Nortriptyline Olanzapine Sertraline Venlafaxine
Smoking Cessation, Substance Abuse, Alcohol Dependence	Short-acting nicotine replacement (e.g., gum or lozenges) Methodone (if enrolled in a maintenance program)	Buprenorphine Buprenorphine/naloxone Disulfiram Naltrexone Bupropion Varenicline
Pain Medications	Butorphanol Morphine Hydromorphone Ibuprofen Celecoxib Flurbiprofen Naproxen Low dose aspirin (75-162 mg)	Codeine Hydrocodone Oxycodone Pentazocine Meperidine Etodolac Fenoprofen Meloxicam Oxaprozin Piroxicam Sulindac Tolmetin Diflunisal Mefenamic acid Ketorolac Carisoprodol High dose aspirin (325 mg)
Galactagogues and Herbal Products	None	Domperidone Metoclopramide Oxytocin Fenugreek Fennel

Citalopram's Updated Product Labeling

By: Amanda Gray, Pharm.D. Candidate

Introduction: Citalopram (Celexa®) is one of the preferred first-line agents in treating major depression from the selective serotonin reuptake inhibitor (SSRI) drug class.[1,2] An important warning listed in the citalopram package insert is in regards to QT interval prolongation.[2] The QT interval is the time it takes for ventricular depolarization and repolarization.[1] The corrected QT interval (QTc) accounts for heart rate and is normally less than 440 milliseconds. A QTc interval above 440 milliseconds is abnormal, while a QTc interval greater than 500 milliseconds is associated with serious cardiovascular adverse events such as torsades de pointes and other cardiac arrhythmias.[1,3] Torsades de pointes, a polymorphic ventricular tachycardia, is a potentially lethal cardiac arrhythmia that creates delayed ventricular repolarization on an electrocardiogram (ECG) and can result in sudden cardiac death.[1] On August 24, 2011, the Food and Drug Administration (FDA) released a statement reporting the use of doses greater than 40 mg of citalopram daily increases a patient's risk for abnormal electrical activity throughout the heart.[4] Consequently, on March 27, 2012, the product labeling for citalopram was updated to highlight new warnings regarding the possibility of QT interval prolongation and torsades de pointes in specific high-risk patients.[5]

New Dosing Recommendations: Post-marketing reports received by the FDA led to increased concern over dose-dependent QT interval prolongation.[5] This resulted in new drug dosage recommendations in the product labeling. Specifically, the recommended starting dose of citalopram is 20 mg by mouth once daily and doses greater than 40 mg per day should not be used. No clear benefit was seen with doses greater than 40 mg daily. Although there is no dosage adjustment associated with renal impairment, caution is recommended in patients with severe renal dysfunction. A maximum dose of 20 mg is recommended for patients with any of these factors: age over 60 years, hepatic impairment, cytochrome-P450 (CYP) 2C19 poor metabolizers, concomitant use of cimetidine or other CYP 2C19 inhibitors.[2]

Warnings Related to QT Prolongation: Caution is highly recommended when using citalopram in certain high-risk patients who have congenital long QT syndrome, bradycardia, recent myocardial infarction, uncompensated heart failure, low potassium and/or low magnesium levels. Caution is advised in patients receiving concomitant medications which prolong the QT interval. If use of citalopram cannot be avoided in these high-risk patients, it is recommended to monitor the ECG and discontinue therapy in patients whose QTc measurements are persistently greater than 500 milliseconds. In high-risk patients, it is recommended to measure potassium and magnesium levels prior to therapy, to correct any imbalances, and to continue watching these levels periodically during therapy. All patients should be educated on signs and symptoms of heart arrhythmias which may include dizziness, palpitations, and syncope.[2]

Summary: Citalopram is now recommended at no greater than 40 mg once daily and has newly emphasized warnings on the dangers of QT prolongation. For patients with any of the following risk factors: age over 60, CYP 2C19 poor metabolizers, hepatic impairment, concomitant use with cimetidine or another CYP 2C19 inhibitor, the maximum dose is 20 mg once daily. If a patient's QTc interval surpasses 500 milliseconds, he or she is at risk of serious cardiovascular events. Serious adverse events occurring with citalopram or any drug can be reported to the FDA via MedWatch at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm.[6]

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