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New Report of PML with Fingolimod (Gilenya®)

The second occurrence of progressive multifocal leukoencephalopathy (PML) has been reported in a patient who had received oral fingolimod (Gilenya®; Novartis) for the treatment of relapsing multiple sclerosis (MS). PML is a rare and serious brain infection that can lead to severe disability or death. It is caused by the John Cunningham (JC) virus, which is common and harmless in most individuals, but can lead to PML in those who are immunocompromised. In 2013, the Food and Drug Administration (FDA) released a safety alert regarding the first report of PML in a patient who received nearly eight months of fingolimod. The patient had been treated with interferon beta-1a, azathioprine, and multiple courses of intravenous corticosteroids, but not natalizumab (Tysabri®; Biogen) prior to fingolimod therapy. In February 2015, Novartis announced that a second case of PML had been reported in a patient who had been treated with fingolimod for over four years. This second patient was not taking any relevant concomitant medications and had no prior exposure to natalizumab. Lymphopenia, a risk factor for PML, was reported during fingolimod treatment. The diagnosis of PML was established based on results from a routine MRI evaluation suggestive of PML lesions and the detection of JC viral DNA in the cerebrospinal fluid. No clinical symptoms of PML were observed. Novartis has not established a causal relationship between fingolimod and the development of PML and continues to evaluate this second case of PML. At this time, the FDA has not published a safety communication regarding this second case report of PML associated with fingolimod therapy.

The risk of PML associated with MS treatment was first identified in 2005 with the use of intravenous natalizumab plus interferon beta-1a. Natalizumab was withdrawn from the market and, after further study, was returned to the market in 2006 as monotherapy for multiple sclerosis (MS) as part of a restricted distribution program. Natalizumab was also FDA approved for the treatment of Crohn's disease (CD) in 2008. Additional cases of PML have been reported in patients treated with natalizumab monotherapy for MS and Crohn's Disease (CD), and who were not on concurrent immunosuppressive therapies. Patients who are at greater risk for PML, if they have received natalizumab for more than two years, are on immunosuppressant therapy or have tested positive for JC virus antibodies.

In November 2014, the FDA issued a safety alert regarding the first confirmed case of PML in a patient treated with oral dimethyl fumarate (Tecfidera®; Biogen) for MS. The patient had experienced prolonged lymphopenia, did not have prior natalizumab exposure, and was not taking other drugs known to affect the immune system. As a result of this case, warnings for the risk of PML were added to the dimethyl fumarate drug label.

American Academy of Ophthalmology Offers Tips on Glaucoma Treatment Adherence

Glaucoma is the leading cause of irreversible blindness in the United States (US); however, when treated early, vision loss can be prevented. Unfortunately, over half of all patients treated do not properly adhere to their prescribed treatment regimens because of cited reasons, such as difficulty in administration and forgetfulness. The American Academy of Ophthalmology (AAO) released tips to help overcome these treatment challenges, many of which can also be helpful to patients using other ophthalmic agents.

Drug Information Highlights

- The fluoroquinolone antibiotic ciprofloxacin (Cipro®; Bayer) received approval for treatment and prophylaxis of plague due to *Yersinia pestis*. Ciprofloxacin is also indicated to treat infections caused by susceptible organisms of the genitourinary and respiratory tracts, skin, bone, and joints.
- The FDA has granted Pharmacicyclics' oral kinase inhibitor ibrutinib (Imbruvica®) breakthrough therapy designation for use in patients with the rare cancer Waldenström's macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma. Ibrutinib is also indicated for use in patients with mantle cell lymphoma and chronic lymphocytic leukemia.
- Celgene's oral thalidomide analogue, lenalidomide (Revlimid®) has gained FDA approval to include patients newly diagnosed with multiple myeloma (MM) in combination with dexamethasone. Previously, approval was granted only for use in patients with MM who had received at least one prior therapy. It is also indicated for treatment of transfusion-dependent anemia due to myelodysplastic syndromes, and progressive/relapsed mantle cell lymphoma after two prior therapies, one of which included bortezomib.
- The central nervous system stimulant, lisdexamfetamine dimesylate capsules (Vyvanse®; Shire), has gained the indication for the treatment of moderate to severe binge eating disorder (BED) in adults. Lisdexamfetamine is the first drug in its class approved for BED. Lisdexamfetamine is also indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 to 17 years old. Lisdexamfetamine dimesylate is a schedule II controlled substance.
- The FDA approved ranibizumab (Lucentis®; Genentech), an anti-VEGF antibody fragment to treat diabetic retinopathy in patients with diabetic macular edema, a leading cause of blindness in the US. Ranibizumab is administered by an intravitreal injection once monthly by a trained physician. This agent is also indicated for the treatment of wet age-related macular degeneration, macular edema following retinal vein occlusion, and diabetic macular edema.
- The FDA has expanded the indication for the oral anticonvulsant drug, rufinamide (Banzel®; Eisai), for use in children as young as one

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Patients should be upfront with their physicians regarding missed doses, which can lead to disease progression, and should be knowledgeable of what to do if a missed dose occurs. Adequate support from family or friends is important for patients who forget doses and/or have difficulty administering the drops. Memory aids, such as linking the time to administer the eye drops with another daily task, are also useful to avoid missed doses. Also, approximately 30 percent of patients treated for glaucoma do not administer the drops properly. Patients should be instructed to create a pocket to administer the eye drops by gently pulling and pinching the lower lid, administer the drop, close their eyes, do not blink, and apply pressure on the inner corner of the eye for two to three minutes. Patients should understand their insurance plans' early refill policy. For example, Medicare Part D allows prescriptions to be refilled once 70 percent of the drug is predicted to have been used. This is particularly important when the patient is learning how to administer the drops as medication waste can occur. In addition, the AAO does not recommend the use of marijuana to replace glaucoma medications to treat the condition, as it is much less effective compared to FDA-approved agents and can cause memory loss, which could further lead to missed doses.

FDA Guidance on Direct-to-Consumer Printed Advertisements

The FDA oversees the labeling and advertising of prescription drugs. The agency recently issued revised draft guidance to their 2004 Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements. In general, printed advertisements for prescription medications, including those in magazines and newspapers, must contain a consumer briefing summary that includes an accurate description of the product's established name, composition, side effects, contraindications and effectiveness, as well as a statement urging the consumer to report negative side effects to the FDA. This is generally achieved using the full risk-related sections of the prescribing information. However, the FDA believes that this is not the best approach since many consumers lack the technical knowledge to understand the information provided. The FDA suggests that the information should be presented in a reader-friendly manner, targeted to an audience with a wide range of literacy skills while avoiding the use of scientific and medical terms. The FDA advises that the consumer briefing summary should provide clinically significant information on the most serious and most common risks associated with use of the product. Printed advertisements should instruct the consumer of the indications for use, all contraindications, the most common and serious adverse reactions, and the most clinically significant warnings and precautions, including the seriousness of risk (debilitating, life-threatening, irreversible), information that would affect a decision to take the drug, such as use in special populations, monitoring requirements, and ways to prevent harm. Information that may be omitted is dosage and administration, and clinical pharmacology. A statement should also be included advising the consumer to speak to his or her health care provider for more complete details. In addition, the FDA believes that the manner that the information is presented can play a role in comprehension of the material. For example, the use of bullets, text boxes, and a question/answer format can increase a consumer's understanding. Advertisements via radio and television media are not addressed in this guidance.

FDA Draft Guidance for Compounding of Human Drugs

In November 2013, as a response to contaminated compounded drug products that led to deaths from fungal meningitis, Congress enacted the Drug Quality and Security Act (DQSA) and created the new Section 503B of the federal Food, Drug, and Cosmetic (FD&C) Act. The DQSA established an oversight of compounding drugs on a small scale at the state level, while giving authority over the manufacture and distribution of compounded drugs to the FDA.

In February 2015, the FDA released five draft documents regarding drug compounding and repackaging that applies to pharmacies, federal facilities, outsourcing facilities and physicians. The draft documents provide information for compounders that are considering registering as an outsourcing facility under Section 503B of the FD&C Act. Also, industry guidance is provided regarding the repackaging of certain human drug products, the mixing, diluting, or repackaging of biological products outside the scope of an approved biologics license application, and adverse event reporting. Finally, a memorandum of understanding (MOU) between a state and the FDA was also drafted detailing the state's responsibilities regarding investigating and responding to complaints relating to interstate distribution of compounded human drug products. The draft documents are available for public comment for 90 days, with the exception of the MOU, which is available for 120 days.

year old as adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome. Previously, this agent was approved in patients ages 4 years and older.

- The FDA has approved a new formulation of Zogenix's hydrocodone bitartrate extended-release capsules (Zohydro® ER), which uses BeadTek™ technology that provides abuse-deterrent properties. Zohydro ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment. Zogenix plans to submit data from their Human Abuse Liability studies in the second half of 2015 to support abuse-deterrent claims in the product labeling. The new formulation forms a viscous gel when crushed and dissolved in liquids or solvents. Hydrocodone bitartrate is a schedule II controlled substance.
- The FDA has determined that Upsher-Smith's 1% testosterone gel, Vogelxo™ unit-dose tubes and packets are therapeutically equivalent (AB-rated) to Testim® testosterone gel. Vogelxo and its authorized generic provide once-daily dosing for the treatment of low testosterone levels in adult males. Both Vogelxo and its generic are also available as a metered-dose gel pump. Testosterone gel is classified as a controlled substance (CIII).

Pipeline News: Upcoming Prescription Drug User Fee Acts (PDUFA) Dates

- **March 2015:** Albuterol metered-dose powder for inhalation (MDPI); short-acting beta-2 agonist; bronchospasm, including exercise-induced; Teva.
- **March 8, 2015:** Isavuconazole; isavuconazonium sulfate; oral and intravenous triazole antifungal; invasive aspergillosis and invasive mucormycosis; Astellas/Basilea.
- **March 17, 2015:** Kalydeco®; ivacaftor; oral cystic fibrosis transmembrane conductance regulator (CFTR) potentiator; cystic fibrosis in patients 2 to 5 years of age with G551D CFTR gene mutations; Vertex.
- **March 29, 2015:** MNK-155; oral controlled-release hydrocodone/acetaminophen abuse-deterrent formulation; opioid agonist; moderate to severe acute pain; Mallinckrodt/Depomed.
- **March 30, 2015:** Eylea®; intravitreal aflibercept; VEGF inhibitor; diabetic retinopathy associated with diabetic macular edema; Regeneron.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
atazanavir/ cobicistat	Evotaz™	The FDA approved Evotaz, a fixed-dose combination of a protease inhibitor, atazanavir, and a pharmacokinetic enhancer, cobicistat, for use with other antiretroviral agents for the treatment of HIV-1 infection in adults. Concurrent use is contraindicated with certain drugs for which altered plasma concentrations may result in serious adverse reactions or loss of virologic response as listed in the package insert. Evotaz is dosed once daily with food. Tablets containing 300 mg of atazanavir and 150 mg of cobicistat are available. The individual components of Evotaz are also available under other trade names for HIV treatment.	Bristol Myers Squibb	FDA NDA approval 01/29/2015
darunavir/ cobicistat	Prezcobix™	Prezcobix, darunavir, and cobicistat are a fixed-dose combination containing a protease inhibitor and pharmacokinetic enhancer for the treatment of HIV-1 infection in adults. Darunavir and cobicistat are currently available as single ingredient tablets for the treatment of HIV. Concomitant use with certain drugs may alter plasma concentrations and lead to serious and/or life-threatening events; see package insert for contraindications. Liver function tests are recommended due to the potential for drug-induced hepatitis and liver injury. Prezcobix is available as tablets containing 800 mg of darunavir and 150 mg of cobicistat, and should be administered once daily with food.	Janssen	FDA NDA approval 01/29/2015
empagliflozin/ linagliptin	Glyxambi®	The FDA has approved the fixed-dose combination of empagliflozin, a sodium glucose co-transporter-2 (SGLT2) inhibitor and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor (Glyxambi) as an adjunct to diet and exercise for the treatment of adults with type 2 diabetes mellitus. Glyxambi is contraindicated in patients with severe renal impairment, end-stage renal disease, or who are on dialysis. There have also been postmarketing reports of acute pancreatitis in patients taking linagliptin, a component of Glyxambi. The recommended starting dose is 10 mg empagliflozin/5 mg linagliptin once daily. It is available in two combination strengths, 10 mg/5 mg and 25 mg/5 mg of empagliflozin and linagliptin, respectively.	Boehringer Ingelheim	FDA NDA approval 01/30/2015
palbociclib	Ibrance®	Palbociclib (Ibrance) is a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor for the treatment of estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer. Palbociclib was approved under FDA's accelerated approval program and was granted breakthrough therapy designation. Warnings include neutropenia, infection, and embryo fetal toxicity. The starting dose is 125 mg once daily with food for 21 days followed by seven days off treatment. It is available as 75 mg, 100 mg, and 125 mg capsules.	Pfizer	FDA NDA Priority approval 02/03/2015
lenvatinib	Lenvima™	Lenvatinib (Lenvima), an oral multiple receptor tyrosine kinase (RTK) inhibitor, has been approved for the treatment of locally recurrent or metastatic, progressive radioactive iodine-refractory differentiated thyroid cancer (DTC). Lenvatinib also received orphan drug status. Careful monitoring is recommended for cardiac, liver, and kidney function. Treatment should be withheld for grade 3 or 4 cardiac failure or renal impairment, reversible posterior leukoencephalopathy syndrome or hemorrhagic events. Lenvatinib is available as 4 mg and 10 mg capsules, and recommended dosing is 24 mg once daily. Daily dose should be adjusted to 14 mg in patients with severe renal or hepatic impairment.	Eisai	FDA NDA Priority approval 02/13/2015
panobinostat	Farydak®	Panobinostat (Farydak), the first histone deacetylase (HDAC) inhibitor is approved to treat multiple myeloma in combination with bortezomib and dexamethasone for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. Panobinostat was given accelerated approval based on progression-free survival and also received orphan drug designation. This agent carries a boxed warning for severe diarrhea and severe and fatal cardiac ischemic events, arrhythmias, and electrocardiogram changes. Panobinostat is administered as 20 mg once every other day for 3 doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for 8 cycles. An additional 8 cycles should be considered for patients with clinical benefit. It will be available in 10 mg, 15 mg and 20 mg capsules.	Novartis	FDA NDA Priority approval 02/13/2015

Erratum: The February 2015 Clinical Alert edition included pipeline information for hydrocodone bitartrate ER (Zohydro® ER) but did not note the filing was for a new formulation utilizing abuse-deterrent technology. Both the current and abuse-deterrent formulations are indicated for the management of severe pain. Since the publication of the February 2015 Clinical Alert, the abuse-deterrent Zohydro ER formulation has received FDA approval as noted in the March 2015 Clinical Alert edition.

References

<https://www.magellanmedicaid.com/news/clinicalalerts.asp>
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www.aao.org
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