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Recently Approved Generic Drugs

February 2021	March 2021	April 2021
Topiramate ER capsules (Qudexy® XR)	Hydrocodone ER tablets (Hysingla® ER)	Macitentan tablets (Opsumit®)
Linaclotide capsules (Linzess®)	Isotretinoin capsules (Absorica®)	Pregabalin ER tablets (Lyrica® CR)
Loteprednol ophthalmic gel (Lotemax®)	Ibrutinib capsules (Imbruvica®)	
Apremilast tablets (Otezla®)		
Droxidopa capsules (Northera®)		

Kansas Drug Utilization Review NEWSLETTER

Issue: Quarter 2 2021

Welcome to the quarterly edition of the *Kansas Drug Utilization Review Newsletter*, published by Health Information Designs, LLC . This newsletter is part of a continuing effort to keep the Medicaid provider community informed of important changes in the Kansas Medical Assistance Program (KMAP).

Legislation

On April 23, 2021, the Ensuring Innovation Act and Advancing Education on Biosimilars Act were signed into law.[1,7]

Ensuring Innovation Act

The Ensuring Innovation Act (EIA) was proposed to increase availability of generic drugs by clarifying the definition of a new chemical entity (NCE) and subsequently redefining the terms for exclusivity extensions.[1]

Background

The Hatch-Waxman Amendments (HWA) of 1984 (also known as the Drug Price Competition and Patent Term Restoration Act) established the approval pathway for generic drugs through an abbreviated new drug application (ANDA).[2] However, since at least 1988, the FDA has used the term "active moiety"[3] to make exclusivity determinations as opposed to the statutory language "active ingredient".[4]

Manufacturers have challenged the FDA's use of the term "active moiety". For example, Abbott Labs was seeking 10-year exclusivity for Depakote® (divalproex sodium) but was awarded 2-year exclusivity instead. The FDA pointed out that the active moiety (valproic acid in Depakene®) was previously approved years prior. A district court ruled in favor of the FDA but was reversed in favor of Abbott in an appellate court.[6]

The EIA amends the Food, Drug, and Cosmetic Act (FDCA) and gives the FDA statutory authority to use the more narrow term "active moiety" instead of the term "active ingredient" in certain situations, including when market exclusivity is being determined.[1-3, 5] The intention of this law is to allow generics to come to market sooner by limiting exclusivity extensions to drugs where minor chemical modifications have been made that may or may not translate to significant differences in therapeutic effect or safety profile.

The EIA potentially accelerates generic availability for the small molecule drug agents in some cases, but this law does not apply to biologic agents. Small molecule agents are regulated by the FDCA, while the more complex biologic agents (and corresponding biosimilars) are regulated under the Public Health Service (PHS) Act.

Advancing Education on Biosimilars Act

The Advancing Education on Biosimilars Act (AEBA) was signed into law at the same time. This legislation was proposed to advance education and awareness about biosimilar agents - including information on biosimilar biological products and interchangeable biosimilar biological

Kansas Department of Health and Environment Website Information

KanCare and Medicaid - Pharmacy
www.kdheks.gov/hcf/pharmacy/

Important Phone Numbers

KMAP PA Phone: 800-933-6593
KMAP PA Fax: 800-913-2229

Aetna PA Pharmacy
Phone: 855-221-5656
Fax: 844-807-8453

Aetna PA Medical
Phone: 855-221-5656
Fax: 855-225-4102

Sunflower PA Pharmacy
Phone: 877-397-9526
Fax: 866-399-0929

Sunflower PA Medical
Phone: 877-644-4623
Fax: 888-453-4756

UHC PA Pharmacy
Phone: 800-310-6826
Fax: 866-940-7328

UHC PA Medical
Phone: 866-604-3267
Fax: 866-946-6474

products. The law requires the FDA to develop and/or improve continuing education programs, establish websites that provide materials for health care providers as well as patients and create other educational tools (e.g., webinars, factsheets, infographics, etc.) as a way to disseminate information regarding biologic agents.[7]

The website(s) may include:[7]

- Explanations of statutory and regulatory terms
- Clarification regarding use of interchangeable biosimilar products
- Information related to the development of biologic agents and relevant clinical considerations (for example, information related to the comparability of biologic products)
- Explanation of the process for reporting adverse events
- Explanation of biosimilars and interchangeable biosimilars, including the standards for review and how each type of biologic is licensed

The ABEA was introduced to increase the use of biosimilars and as a result, promote competition and lower the costs of biologic therapies.[7]

1. S.415 – 117th Congress (2021-2022): A bill to amend the Federal Food, Drug, and Cosmetic Act with respect to the scope of new chemical exclusivity, S.415, 117th Cong (2021).
2. Food and Drug Administration (FDA). Hatch-Waxman Letters.
3. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Guidance for Industry. (Sixth of seven Hatch-Waxman Letters).
4. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).
5. Applications for FDA Approval to Market a New Drug. 21 C.F.R § 314.3 (2021).
6. Abbott Laboratories, Appellant, v. Frank D. Young, Dr., Commissioner, Food and Drug Administration, 920 F.2d 984 (D.C. Cir. 1990). December 7, 1990.
7. S.164 – 117th Congress (2021-2022): Advancing Education on Biosimilars Act of 2021, S.164, 117th Cong (2021).

Current Drug Safety Communications

Lamictal

In March 2021, the FDA published a drug safety warning after a review of study results showed an increased risk of arrhythmias in patients with heart disease taking Lamictal (lamotrigine).[1]

The studies were required by the FDA to look into the effects of lamotrigine on the heart after receiving reports of abnormal electrocardiographic (ECG) findings and other cardiac issues. Studies showed that at therapeutic concentrations, lamotrigine can increase the risk of arrythmias in patients with structural or functional heart disorders, including (but not limited to) heart failure, valvular heart disease and congenital heart disease. Risk of arrythmias increases if used in combination with other agents that block sodium channels in the heart. Prescribers should assess whether the benefits of lamotrigine therapy outweigh the risks.[1]

Further studies will be required for agents in the same drug class to determine if they have similar effects on the heart. These agents include:[1]

Carbamazepine	Lacosamide	Topiramate
Cenobamate	Oxcarbazepine	Zonisamide
Eslicarbazepine	Phenytoin	
Fosphenytoin	Rufinamide	

Previous safety communications issued for lamotrigine:

- Possible association between lamotrigine exposure during pregnancy and oral clefts in newborns (2006)[1]
- Class warning for anti-seizure agents - suicidal thoughts and behavior (2009)[2]
- Aseptic meningitis (2010)[3]
- Serious immune system reaction (2018)[4]

1. U.S. Food and Drug Administration. (2021, March 31). Lamictal (lamotrigine): Drug Safety Communication – Studies Show Increased Risk of Heart Rhythm Problems in Patients with Heart Disease. [Drug Safety Communication].
2. U.S. Food and Drug Administration. (2009, May 5). Suicidal Behavior and Ideation and Antiepileptic Drugs. [Drug Safety Communication].
3. U.S. Food and Drug Administration. (2010, August 12). FDA Drug Safety Communication: Aseptic meningitis associated with use of Lamictal (lamotrigine). [Drug Safety Communication].
4. U.S. Food and Drug Administration. (2018, April 25). FDA Drug Safety Communication: FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal). [Drug Safety Communication].

Xeljanz

When Xeljanz was initially approved in 2011, the Food and Drug Administration (FDA) required the drug company to conduct a long-term safety trial.[1] The primary goal of the study (ORAL Surveillance Study [NCT02092467]) was to evaluate the safety of tofacitinib versus a TNF inhibitor in subjects with rheumatoid arthritis (RA) with at least one additional cardiovascular (CV) risk factor. The primary endpoints were noninferiority of tofacitinib compared to TNFs with regard to major adverse CV events (MACEs) and malignancies.[2]

During the safety trial, an external data safety monitoring committee found an increased risk of blood clots and death with the 10mg twice daily dosage of tofacitinib. This resulted in the FDA issuing a safety warning in February and July 2019.[3] Following this, a boxed warning was added to the tofacitinib prescribing information.[4]

In January 2021, when the trial was complete, it was announced that tofacitinib did not meet the primary endpoints of noninferiority compared to TNF inhibitors. The full study results are not yet available, but preliminary results show a higher occurrence of serious heart-related events and cancer in tofacitinib compared to TNF inhibitors.[5] The FDA has issued a drug safety communication but has not yet issued final recommendations to providers regarding the use of Xeljanz. For now, the FDA advises health care professionals to consider the benefits and risks of tofacitinib when initiating or continuing therapy.[1]

1. U.S. Food and Drug Administration. (2021, February 4). Xeljanz, Xeljanz XR (tofacitinib): Drug Safety Communication – Initial Safety Trial Results Find Increased Risk of Serious Heart-related Problems and Cancer with Arthritis and Ulcerative Colitis Medicine. [Drug Safety Communication].
2. Pfizer, Inc. Safety Study of Tofacitinib Versus Tumor Necrosis Factor (TNF) Inhibitor in Subjects with Rheumatoid Arthritis. NCT02092467.
3. U.S. Food and Drug Administration. (2019, February 25). Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to Investigate. [Drug Safety Communication].
4. U.S. Food and Drug Administration. (2019, July 26). FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR). [Drug Safety Communication].
5. Pfizer. (2021, January 27). Pfizer Shares Co-Primary Endpoint Results from Post-Marketing Required Safety Study of Xeljanz (Tofacitinib) in Subjects with Rheumatoid Arthritis (RA). [Press Release].

Makena

In October 2020, the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) recommended that Makena (hydroxyprogesterone caproate [HPC]) be withdrawn from the market.[1]

In 2011, Makena was approved by the FDA to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.[2] Because the drug was approved through an accelerated pathway, its continued approval was contingent upon whether its confirmatory trial, the PROLONG study, could verify clinical benefit.

PROLONG (NCT01004029) was an international double-blind, placebo-controlled trial with 1708 women enrolled. The study had 2 primary outcomes: preterm birth (PTB) < 35 weeks and neonatal morbidity composite index. The study concluded that there were no significant differences found between HPC and placebo and the CDER concluded that the evidence does not show that Makena is effective for its labeled indication.[1, 3-4]

In March 2021, a meta-analysis of randomized, controlled trials evaluating the use of progestogens for prevention of preterm birth was published. Although there was a trend in favor of efficacy for HPC, the confidence interval for relative risk crossed 1.00, the "line of no effect".[5]

At the time of this writing, Makena and HPC products are still available. Until a final decision is made, the FDA recommends providers discuss the benefits, risks and uncertainties with the patient before initiating therapy.[1]

1. U.S. Food and Drug Administration Center for Drug Evaluation and Research. (2020, October 5). CDER proposes withdrawal of approval for Makena. [Drug Safety Communication].
2. Makena (hydroxyprogesterone caproate) [prescribing information]. Waltham, MA: AMAG Pharmaceuticals, Inc.; November 2020.
3. Blackwell SC, Gyamfi-Bannerman C, Biggio JR, et al. 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial. Am J Perinatol 2020 Jan;37(2):127-136.
4. AMAG Pharmaceuticals, Inc. Confirmatory Study of 17P vs Vehicle for Prevention of Preterm Birth in Women with Previous Spontaneous Preterm Delivery (PROLONG). NCT01004029.
5. The EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomized controlled trials. The Lancet 2021;397(10280):1183-1194.