NOVEMBER 2020

PERSPECTIVE ON THE Rx PIPELINE

Understanding changes in the medication market and their impact on cost and care.

Elixir continuously monitors the drug pipeline. As treatment options change, we evaluate and share our perspective on the clinical benefits, cost effectiveness and overall impact to payers and members. Our Perspective on the Rx Pipeline report provides ongoing actionable insights from our team of clinical experts and the steps we are taking to protect and improve plan performance.

INCLUDED IN THIS EDITION:

- Clinical Pipeline
- Key New Drug Approvals
- New Indications
- Upcoming and Recent Generic and Biosimilar Launches
- FDA Safety Update
- Drug Shortages, Discontinuations and Recalls

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CRAFTED Rx SOLUTIONS

Clinical Pipeline

Inclisiran

Manufacturer: Novartis
Indication/Use: As an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C
Dosage Form: Subcutaneous injection
Pipeline Stage: PDUFA 4Q 2020

The 2019 *Heart Disease and Stroke Statistics* reported by the American Heart Association estimated that 48% of Americans 20 years of age or older have cardiovascular disease (CVD).[1] The standard of care for primary and secondary prevention of CVD is statin therapy. If additional lipid lowering is needed in conjunction with statin therapy, ezetimibe or proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) inhibitors can be added to the regimen.[2] There are currently two injectable PCSK9 inhibitors on the market, Praluent® and Repatha®. These medications are given every two to four weeks. Praluent and Repatha both have an expanded indication to reduce the risk of myocardial infarction, stroke and coronary revascularization in adults with established CVD.[3-4]

Pipeline product inclisiran is a small interfering RNA molecule (siRNA) with a similar mechanism of action to competing PCSK9 inhibitors. It too could be used in conjunction with statin therapy for additional lipid lowering, but this product—given twice yearly—will offer less frequent maintenance injections. However, at the time of the biologic license application (BLA) approval, inclisiran will not have the cardiovascular (CV) mortality benefit included on the labeled indication.[2, 5]

The ORION trials are evaluating the safety and efficacy of inclisiran. The pivotal trials, ORION 10 and 11, evaluated patients with atherosclerotic CVD (ASCVD) or ASCVD risk equivalent. Both trials were double blind, randomized for participants to receive inclisiran or placebo in conjunction with maximally tolerated statin therapy. The primary endpoint was percentage of change in low-density lipoprotein (LDL) from baseline. Results were pooled between the two trials and participants were followed for 17 months to allow them to get to a maintenance injection regimen. A LDL reduction of at least 50% was reached by 88.4% of patients at any time in the study, while 66.4% of the treatment group had at least a 50% reduction in LDL compared to 2.5% in the placebo group at the end of the trial. Cardiovascular risk reduction data is not expected until 2024 from the ORION 4 data.[5-8]

Due to no CV outcomes or labeled indication, it is expected that the uptake of inclisiran may be delayed in comparison to the competition. Even though inclisiran has less frequent administration than its competition, the product requires in-office administration by a healthcare professional, which will most likely be a disadvantage. Cardiologists may be hesitant to start in-office administration when there are FDA-approved products with labeled CV risk reduction. Formulary strategy will also have to be evaluated for coverage of an additional PCSK9 inhibitor.

Glossary of Terms **BLA** - Biologics License Application **NDA** - New Drug Application **PDUFA** - Prescription Drug User Fee Act

Clinical Pipeline

Orladeyo *berotralstat*

Manufacturer: BioCryst
Indication/Use: Prophylaxis against angioedema attacks in hereditary angioedema (HAE)
Dosage Form: Oral
Pipeline Stage: PDUFA 12/03/2020

Hereditary angioedema (HAE) is a very rare autosomal dominant inherited genetic disease and potentially life-threatening condition that occurs in approximately 1 in 10,000 to 1 in 50,000 people.[9] It is characterized by recurrent episodes of angioedema without urticaria, usually affecting the skin, mucosal tissues of the upper respiratory and/or gastrointestinal (GI) tracts. Concern arises when patients experience laryngeal edema/swelling, which can cause difficulty breathing or a GI attack. This may lead to unnecessary abdominal surgery.[10] HAE severity and frequency of attacks can vary patient to patient and there are often "attack triggers," such as hormonal changes, dental procedures, anxiety, stress, minor trauma, surgery, and colds or influenza.[9] HAE may often be misdiagnosed as an allergic reaction or irritable bowel syndrome.[11] It is very important for HAE to be properly diagnosed with a laboratory assessment, as the treatment for mistaken indications are not effective for HAE.

Treatment of HAE involves either treating the attack once it is occurring or using prophylaxis treatment to help prevent or reduce future attacks. Multiple C-1 inhibitors are used to treat HAE attacks or as prevention, such as Berinert®, Haegarda®, Cinryze® and Ruconest®. Kallikrein inhibitors, such as Kalbitor® (treatment) or Takhzyro® (prevention) may also be used. Firazyr® is a bradykinin inhibitor that can be used as a subcutaneous injection to treat HAE attacks. The 2017 World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guidelines recommend that all attacks be considered for on-demand treatment with one of these options.

A patient may use short-term prophylaxis when, for example, they anticipate a planned surgery or dental procedure. Whether a patient is a candidate for long-term prophylaxis may be decided by many factors, such as frequency, severity and location of attacks, access to acute care, comorbid conditions, and individual preferences. The WAO/EAACI 2017 guidelines recommend C1-inhibitors as first-line for long-term prophylaxis.[12] Orladeyo is being studied for prophylaxis of HAE attacks by inhibiting plasma kallikrein, much like Takhyzro and Kalbitor.

Clinical trials are well underway for Orladeyo, which would be the first oral prophylaxis treatment for HAE. APeX-2 is a phase III, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dosage regimens of Orladeyo in preventing HAE attacks. Patients were 12 years of age and older (and ≥ 40 kg) with HAE type 1 or 2 (defined as having a C1-INH functional level and C4 level below the lower limit of normal reference range). This trial enrolled 121 patients who were randomized to Orladeyo 110 mg daily, Orladeyo 150 mg daily or placebo. The primary endpoint was investigator-confirmed HAE attack during the 24-week treatment period. The Orladeyo 150 mg group showed a reduction in rate of HAE attacks of 44.2% ($p<0.001$). The Orladeyo 110 mg group did not have a statistically significant reduction. Also, results showed Orladeyo 150 mg once-daily reduced patients' rate of on-demand medications per 28 days by 53.6% ($p<0.001$) compared to placebo. The most frequent adverse drug reactions were mild-to-moderate gastrointestinal events. The second study APeX-S, an extension trial, will evaluate the long-term safety and efficacy of daily oral Orladeyo for 96 weeks in patients with type 1 and 2 HAE. APeX-S is still currently being conducted, but interim results are showing a positive trend to attack reduction/prevention.[13, 14]

Orladeyo may offer the first oral prevention treatment for HAE with a similar mechanism of action as preventive Takhyzro for providers who would like to use a plasma kallikrein inhibitor or an oral medication to help patients prevent HAE attacks. However, head-to-head trials comparing Orladeyo to other prophylactic HAE treatments have yet to occur and would be helpful to define Orladeyo's place in therapy.

Clinical Pipeline

RM-493 *setmelanotide*

Manufacturer: Rhythm Pharmaceuticals, Inc.
Indication/Use: Pro-opiomelanocortin (POMC) deficiency obesity and leptin receptor (LEPR) deficiency obesity
Dosage Form: Subcutaneous injection
Pipeline Stage: PDUFA 11/27/2020

RM-493 is a very specific weight loss treatment for obesity due to rare genetic disorders and was granted Breakthrough Therapy Designation by the FDA. While there are multiple genetic obesity conditions that RM-493 may be used to treat, current clinical trials are evaluating its use in the treatment of pro-opiomelanocortin (POMC) deficiency and Leptin receptor (LEPR) deficiency obesity, inherited as autosomal recessive genetic disorders. LEPR and POMC deficiency obesity have a low estimated prevalence of 100 to 500 (POMC) and 500 to 2,000 (LEPR) people in the United States.[15] Alström syndrome, a heterozygous genetic disorder, and Bardet-Biedl syndrome are additional indications Rhythm Pharmaceuticals will seek in the near future. Other heterozygous MC4R mutations are the most common forms of genetic obesity, found in 2% to 5% of subjects with extreme pediatric obesity, and may impact more patients than LEPR or POMC.[16, 17]

Patients with genetic disorders of obesity are born at a normal weight, but obesity begins in the first few months and continues throughout the patient's life. Genetic disorders of obesity present with a childhood BMI ≥ 95th percentile for age.[18] In both POMC and LEPR, patients have an excessive urge to eat, known as hyperphagia. POMC is a prohormone regulating the upstream release of adrenocorticotropic hormone (ACTH) from the pituitary and alpha-MSH from the hypothalamic neurons and skin.[15, 19] In POMC deficiency obesity, patients have decreased levels of ACTH and alpha-MSH (which relays the anorexic effects of leptin) and decreased activation of the melanocortin-4 receptor (MC4R) pathway. Those with POMC deficiency must be treated with hydrocortisone early to combat decreased ACTH. Reduced alpha-MSH may be the cause of obesity. Patients with LEPR deficiency obesity have variants in the LEPR gene causing defects in the leptin receptor, leading to a lack of response to leptin and causing increased hunger and decreased satiety from impaired alpha-MSH activation downstream.[19, 20]

RM-493 is an agonist of the MC4R, which regulates hunger via leptin release from adipose tissue. Activating MC4R reduces hunger and increases energy expenditure. The vast majority of obese patients are not leptin deficient or due to ACTH production.

In two phase III, single arm, open-label, multicenter studies the primary endpoint of ≥ 10% weight loss compared to baseline at approximately one year was reached for eight out of 10 POMC patients and five out of 11 LEPR patients. The POMC population had a mean weight loss of 70.2 pounds over a year and LEPR patients lost 36.8 pounds over a year. POMC mean reduction from baseline in body weight was -25.4% (90% CI: -28.80, -21.98; p <.0001). LEPR mean reduction from baseline in body weight was -12.5% (90% CI: -16.10, -8.83; p <.0001). The most common adverse events were injection site reactions, nausea and hyperpigmentation/skin disorders.[21, 22]

Patients with genetic disorder obesity have limited pharmaceutical options, as exercise and diets usually fail to cause successful weight loss. Often the next step for these patients is bariatric surgery. RM-493 is showing effective weight loss in these rare genetic obesity indications. It is always important to consider side effects and safety. The leptin pathway has the possibility for unintended side effects of blood pressure increases and renal alterations.[20] It is also notable that while some payers consider obesity reduction medication cosmetic, obesity continues to have a high correlation to worsening health measures, such as increased risk of hypertension, diabetes and cardiovascular disease. Pharmaceutical companies are continuing research to provide additional weight loss pharmaceutical options for patients.

Key New Drug Approvals

Evrysdi™ *risdiplam*

Manufacturer: Genentech
Indication/Use: Spinal muscular atrophy (SMA)
Dosage Form: Oral solution
Traditional or Specialty: Specialty

On August 7, 2020, the FDA granted approval to Evrysdi, the first oral disease-modifying therapy for SMA in patients two months of age and older. Evrysdi is given daily, but offers an easier administration than Spinraza®, which is intrathecal. Zolgensma®, a gene therapy for SMA, is approved only in those two years of age and younger. Evrysdi may find its place to treat those that are not eligible for Zolgensma or have less severe forms of SMA.

For more information: https://www.evrysdi.com/about-evrysdi.html

Kesimpta® *ofatumumab*

Manufacturer: Novartis
Indication/Use: Multiple sclerosis (MS)
Dosage Form: Subcutaneous injection
Traditional or Specialty: Specialty

Ofatumumab was previously approved as Arzerra® for the oncology indication of chronic lymphocytic leukemia. Ofatumumab as Kesimpta was granted FDA approval for clinically isolated syndrome, relapsing-remitting disease and active secondary progressive MS on August 20, 2020. Kesimpta is an anti-CD20 monoclonal antibody, binding to CD20+ B-cell for lysis, which may subsequently reduce inflammation in MS. It was not granted FDA approval for the indication of primary progressive MS that Ocrevus (ocrelizumab), the first anti-CD20 monoclonal antibody indicated for MS, carries. Kesimpta can be self-administered monthly after induction, where as Ocrevus is an intravenous infusion every six months.

For more information: https://www.kesimpta.com/

Mycapssa® *octreotide*

Manufacturer: Chiasma
Indication/Use: Acromegaly
Dosage Form: Oral capsule
Traditional or Specialty: Specialty

Mycapssa was FDA approved on June 26, 2020 for long-term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide. Mycapssa contains octreotide, which is delivered via a capsule with transient permeability enhancer (TPE), a technology that allows peptides and proteins that are normally disintegrated in the stomach to be appropriately absorbed in the small intestine. This product is the next step in therapy, once a patient is stable on octreotide or lanreotide injections.

For more information: https://chiasma.com/octreotide-capsules/

Key New Drug Approvals

Veklury® *remdesivir*

Manufacturer: Gilead
Indication/Use: Coronavirus disease 2019 (COVID-19) requiring hospitalization
Dosage Form: Intravenous infusion
Traditional or Specialty: Traditional

On October 22, 2020, the FDA approved Veklury as the first treatment for COIVID-19. Veklury is approved for administration in a hospital or healthcare setting for adult and pediatric patients (12 years of age and 40 kilograms). This product was originally granted Emergency Use Authorization on May 1, 2020, but has now been granted FDA approval for hospital administration. This drug utilization will most likely be seen on the medical spend.

For more information: https://www.fda.gov/drugs/drug-safety-and-availability/fdas-approval-veklury-remdesivir-treatment-covid-19-science-safety-and-effectiveness

Viltepso® *viltolarsen*

Manufacturer: NS Pharma, Inc.
Indication/Use: Duchenne muscular dystrophy (DMD)
Dosage Form: Intravenous injection
Traditional or Specialty: Specialty

On August 12, 2020, the FDA approved Viltepso as another intravenous medication for DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. It joins Exondys (DMD exon 51 skipping) and Vyondys (DMD exon 53 skipping). About 8% of the DMD population is exon 53 skipping. Vyondys is indicated for those six years of age and older, while Viltepso was studied in males four years of age and older. Like other current antisense oligonucleotides, Viltepso used a surrogate marker of increased dystrophin expression to evaluate effectiveness. The FDA concluded that an increase in dystrophin production seen in Viltepso is reasonably likely to predict clinical benefit. Viltepso must be given by a healthcare professional in the home or at a medical facility.

For more information: https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation

Key New Drug Approvals

Winlevi® *clascoterone*

Manufacturer: Cassiopea
Indication/Use: Acne vulgaris
Dosage Form: Topical cream
Traditional or Specialty: Traditional

Approved on August 26, 2020, Winlevi is an androgen receptor inhibitor for the treatment of acne in men and women 12 years of age and older. Acne is targeted in four ways: excess sebum production, inflammation, bacterial growth and hyperproliferation of the skin.[23] Winlevi targets inflammation and sebum production. Similarly, oral spironolactone has been used off label in women only to inhibit androgen activity (by decreasing testosterone), but women should consider concurrent contraceptive therapy to prevent pregnancy and regulate menses. Select oral contraceptives have also been used to improve acne in some female patients. Winlevi had a mild adverse event profile. Winlevi is the first new mechanism of action FDA-approved medication for acne in over three decades.

For more information: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trial-snapshot-winlevi

Xywav™ *calcium oxybate, magnesium oxybate, potassium oxybate, sodium oxybate*

Manufacturer: Jazz Pharmaceuticals
Indication/Use: Cataplexy or excessive daytime sleepiness associated with narcolepsy
Dosage Form: Oral solution
Traditional or Specialty: Specialty

Xywav, which is marketed to have 92% less sodium than Xyrem® (sodium oxybate alone) was approved by the FDA on July 21, 2020. Xyrem's package insert notes that patients with sensitivities (heart failure, hypertension or renal impairment) to high sodium intake should consider the nightly exposure of sodium in each dose of Xyrem with their daily dietary intake. For example, Xyrem 7.5 g per night contains 1,400 mg of sodium.[24] The American Heart Association suggests no more than 2,300 mg per day of sodium, with ideal intake being near 1,500 mg daily.[25] The same dose of Xywav can be used in those transitioning from Xyrem. Notably, Xywav still carries the controlled substance requirement due to risk of abuse/misuse and still may cause central nervous system depression.

For more information: https://www.xywavhcp.com

New Indications

Epidiolex® *cannabidiol*

Manufacturer: GW Pharmaceuticals
Indication/Use: Lennox-Gastuat syndrome and Dravet syndrome
Dosage Form: Oral solution
Traditional or Specialty: Specialty
Date of Original Approval: 06/25/2018

Epidiolex received FDA approval to treat seizures associated with tuberous sclerosis in patients one year of age and older. Tuberous sclerosis causes benign tumors to grow in organs, such as the brain, heart, skin, lung, eyes and kidneys. Tuberous sclerosis tends to lead to central nervous system symptoms, such as, but not limited to, seizures, behavioral problems and impaired intellectual development.[26] Frequency is about 1 in 6,000 newborns in the United States, and severity of the disease varies from mild to severe.[27] Epidiolex also has indications for epilepsy, infantile spasms and Rett syndrome in the phase III pipeline. It may also be noted that as of April 2020, the schedule V controlled substance granted by the Drug Enforcement Administration was removed for Epidiolex.

For more information: https://www.fda.gov/news-events/press-announcements/fda-approves-new-indication-drug-containing-active-ingredient-derived-cannabis-treat-seizures-rare

Kalydeco® *ivacaftor*

Manufacturer: Vertex Pharmaceuticals, Inc.
Indication/Use: Cystic fibrosis
Dosage Form: Oral tablets and granules
Traditional or Specialty: Specialty
Date of Original Approval: 03/17/2015

On September 24, 2020, Kalydeco was granted FDA approval for patients four months of age and older with cystic fibrosis who have one mutation in the CFTR gene that is responsive to ivacaftor. Kalydeco has the youngest FDA approval indication of all cystic fibrosis transmembrane regulator protein treatments.

For more information: www.kalydeco.com

New Indications

Nucala® *mepolizumab*

Manufacturer: GlaxoSmithKline
Indication/Use: Add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype and treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)
Dosage Form: Subcutaneous injection
Traditional or Specialty: Specialty
Date of Original Approval: 11/04/2015

As of September 25, 2020, Nucala is FDA indicated for adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for greater than or equal to six months without an identifiable non-hematologic secondary cause. HES is a rare blood disorder where patients usually have more than 1,500 eosinophils/microliter in their blood and a cause cannot be identified (for most individuals eosinophil/microliter is 500 or less).[28] Excessive eosinophils can cause undesirable symptoms, such as fatigue, hives and itching, cough, dizziness, and fever, but most concerning is the possibility of organ dysfunction from chronic inflammation in those with HES.

For more information: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-group-rare-blood-disorders-nearly-14-years

Spravato® *esketamine*

Manufacturer: Janseen Pharmaceuticals, Inc.
Indication/Use: Adults with treatment-resistant depression
Dosage Form: Nasal spray
Traditional or Specialty: Traditional
Date of Original Approval: 03/05/2019

On July 31, 2020, the FDA granted Spravato the new indication to treat depressive symptoms in adults with major depressive disorder (MDD) with suicidal thoughts or actions. Patients in the ASPIRE I and II studies were initially hospitalized. Spravato must be taken with an oral antidepressant. Treatment with Spravato for MDD is for four weeks and then a treatment plan should be evaluated along with need for continued treatment.

For more information: https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified

https://www.jnj.com/janssen-seeks-expanded-use-of-spravato-esketamine-nasal-spray-in-europe-as-a-treatment-for-depressive-symptoms-in-adults-with-major-depressive-disorder-who-have-current-suicidal-ideation-with-intent

New Indications

Stelara® *ustekinumab*

Manufacturer: Janssen
Indication/Use: Patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, active psoriatic arthritis alone or in combination with methotrexate, moderately to severely active Crohn's disease, and ulcerative colitis
Dosage Form: Subcutaneous injection
Traditional or Specialty: Specialty
Date of Original Approval: 09/23/2016

Stelara was granted approval by the FDA for use in pediatric patients as young as six years of age with moderate to severe plaque psoriasis on July 19, 2020. Taltz® received an indication for children six to 17 years of age in April 2020. Enbrel® is FDA approved for those at least four years of age. Topical corticosteroids are the primary treatment for children with psoriasis. When the disease presents as moderate or severe that cannot be controlled with topical treatment a systemic biologic may be considered.

For more information: https://www.stelarainfo.com/plaque-psoriasis/

Upcoming and Recent Generic and Biosimilar Launches

Brand Name	Generic Name	# of Manufacturer Entrants	Indication	Launched or Anticipated Launch Date
Atripla®	efavirenz, emtricitabine, tenofovir disoproxil fumarate	1	HIV-1 infection and treatment	Launched
Monurol®	fosfomycin tromethamine	1	Uncomplicated urinary tract infections	Launched
Truvada® (200 mg/300 mg)	emtricitabine, tenofovir disoproxil fumarate	1	HIV-1 infection and treatment and HIV pre-exposure prophylaxis	Launched
KUVAN® (powder and tablet)	sapropterin dihydrochloride	1, 2	Hyperphenylalaninemia	Launched
Tykerb™	lapatinib ditosylate	1	Breast cancer	Launched
Ferriprox® (tablet)	deferiprone	1	Transfusional iron overload	Launched
Zorvolex®	diclofenac	1	Osteoarthritis	Launched
Bethkis®	tobramycin	2	Treatment of infection associated with cystic fibrosis	Launched
Emtriva (capsules)	emtricitabine	1	HIV-1 infection and treatment	Launched
Moviprep®	ascorbic acid, polyethylene glycol 3350, potassium chloride, sodium ascorbate, sodium chloride, sodium sulfate	1	Bowel cleansing	Launched
Doryx® (80 mg)	doxycycline hyclate	1	Treatment of infection, acne and prophylaxis of malaria	Launched

Upcoming and Recent Generic and Biosimilar Launches

Brand Name	Generic Name	# of Manufacturer Entrants	Indication	Anticipated Launch Date
Semglee™ (biosimilar for Lantus® vial and Lantus® Solostar®)	insulin glargine	1	Diabetes mellitus types 1 and 2	Launched
Kerydin®	tavaborole	5+	Onychomycosis	Launched
Risperdal Consta®	risperidone	TBD	Schizophrenia, bipolar disorder	11/26/2020
Saphris®	asenapine maleate	5+	Schizophrenia, bipolar disorder	12/10/2020
Chantix®	varenicline tartrate	4	Smoking cessation	4Q 2020
Entereg®	alvimopan	1	Postoperative ileus	2H 2020
Tirosint®	levothyroxine sodium	1	Hypothyroidism	2H 2020
Vascepa®	icosapent ethyl	4	Hypertriglyceridemia, cardiovascular risk reduction with mild hypertriglyceridemia	2H 2020
Byetta®	exenatide synthetic	TBD	Diabetes mellitus type 2	2020
Kaletra® (tablets)	lopinavir, ritonavir	5+	HIV-1 infection and treatment	2020
Noxafil® (suspension)	posaconazole	3	Candidiasis, oropharyngeal, invasive fungal infections, prophylaxis	2020
Omnaris®	ciclesonide	1	Seasonal and perennial allergic rhinitis	2020
Restasis®	cyclosporine	TBD	Increase tear production for those with Keratoconjunctivitis sicca	2020

Upcoming and Recent Generic and Biosimilar Launches

Brand Name	Generic Name	# of Manufacturer Entrants	Indication	Launched or Anticipated Launch Date
Syndros®	dronabinol	TBD	Anorexia in patients with AIDS, chemotherapy-induced nausea and vomiting	2020
Ultravate® (lotion)	halobetasol propionate	1	Plaque psoriasis	2020
Vivlodex®	meloxicam	TBD	Osteoarthritis	2020

FDA Safety Updates

Drug Safety Communication

Amputation Boxed Warning Removed for Diabetes Medicine Canagliflozin

On August 26, 2020, the FDA announced the positive change of the removal of the Boxed Warning for canagliflozin (Invokana, Invokamet, Invokamet XR). In 2017, the FDA required that a black box for "risk of leg and foot amputation" be added to canagliflozin prescribing information. Most recent clinical trials suggest that when appropriately monitored, the risk of amputation is lower than previously reported and the drug has significant benefits for heart and kidney disease, therefore, the risk of amputation has been moved to the Warning and Precautions section of the prescribing information. Healthcare professionals should be monitoring diabetic patients' feet and legs and continuing to assess the risk and need for treatment.

For more information:
https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin

FDA Requiring Boxed Warning to Improve Safe Use of Benzodiazepine Drug Class

The FDA states that 92 million benzodiazepine prescriptions were dispensed from U.S. outpatient pharmacies in 2019, and data from 2018 show that approximately 50% of benzodiazepine prescriptions were for a duration of two months or longer. On September 23, 2020, the FDA released a safety communication that Boxed Warnings will be updated for all benzodiazepine medication. The FDA intends for the update to address the serious risk of physical dependency/addiction, abuse and withdrawal that may occur with benzodiazepine use.

For more information:
https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class

FDA Warns About Serious Problems with High Doses of the Allergy Medicine Diphenhydramine (Benadryl)

A recent social media challenge, known as the Benadryl Challenge, is leading to serious adverse events and death in teenagers. Excessive intake of diphenhydramine can lead to seizures, heart problems, coma and death. The medication is commonly used to treat symptoms such as runny nose and sneezing due to allergies and common colds. Parents may want to monitor and keep diphenhydramine out of the reach of children and teens. Prescribers should be aware of diphenhydramine as a possible suspect of an overdose. The FDA is investigating reports and will provide an update in the future.

For more information:
https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-problems-high-doses-allergy-medicine-diphenhydramine-benadryl

Drug Shortages, Discontinuations and Recalls

Veklury (remdesivir)

Recently, the FDA approved remdesivir to treat all hospitalized COVID-19 patients 12 years of age (at least 40 kg) and older. As noted earlier, it was first given Emergency Use Authorization (EUA) by the FDA in May 2020. Gilead's approval of remdesivir was an expanded indication beyond the first EUA granted use and allows for a larger pool of remdesivir patients. As of October 1, 2020, the United States government is no longer directing allocation of remdesivir and Gilead will distribute to hospitals and healthcare facilities.

At this time, there is no remdesivir shortage or access issues in the United States. Gilead does not have concerns of producing sufficient quantities of Veklury to meet COVID-19 demands. Other countries are experiencing remdesivir shortages, such as Canada and the United Kingdom. Gilead is working to increase production to meet the global need.

For more information: https://www.fda.gov/media/137574/download

https://www.hhs.gov/about/news/2020/10/01/veklury-remdesivir-available-directly-distributor-following-trump-administrations-successful-allocations.html

https://www.gilead.com/purpose/advancing-global-health/covid-19/working-to-supply-remdesivir-for-covid-19

Makena

The FDA Center for Drug Evaluation and Research (CDER) proposed that Makena be withdrawn from the market due to lack of clinical benefit found in post marketing studies, questioning Makena's effectiveness. Makena was approved under accelerated approval to reduce the risk of preterm birth in a singleton pregnancy for women who previously had a spontaneous preterm birth before week 37 of pregnancy. This request pertains to the brand and generic formulation of hydroxyprogesterone caproate injection. Makena will remain available until either the manufacturers decide to remove the medication or the FDA mandates removal. A hearing can be requested by AMAG Pharmaceuticals to contest the removal. Pending possible removal from the market, providers should explain to their patients the questionable efficacy that Makena may offer.

For more information: https://www.fda.gov/drugs/drug-safety-and-availability/cder-proposes-withdrawal-approval-makena

Nitroamine Levels in Metformin

Nitroamines (NDMA) are a byproduct impurity being found in some medications under FDA investigation. People are commonly exposed to NDMA in water and foods. Daily intake of nitroamines over long periods of time may cause adverse events, but acceptable daily intake limits have been set (0.096 micrograms or 0.32 parts per million (ppm)) and daily exposure to these acceptable limits over 70 years is not expected to result in cancer.

The FDA has been evaluating NDMA in human drugs since the previous recall of angiotensin II receptor blockers and ranitidine medication. In February 2020, the FDA posted laboratory testing results for NDMA levels in metformin. Since the press release in May 2020, numerous manufacturers have recalled lots of metformin due to levels of NDMA above acceptable intake limits. The FDA is requesting all manufacturers of metformin ER test at-risk product batches for excessive NDMA before releasing medication to the public. Excessive NDMA batches should be held and the FDA informed by the manufacturers. Metformin ER is not currently in shortage, as not all manufacturer results have NDMA in their metformin, but possible shortages should be monitored. A list of metformin products affected by the recall can be found at the link below. Patients taking prescription medications should not stop their medication, but should talk to a healthcare professional about any concerns.

For more information: https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-metformin-products

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin

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Clinical efficacy and safety, balanced with a drug's value, are always at the forefront in the Elixir formulary decisions and pipeline planning. The rationale for those decisions may go beyond the use of the FDA's labeled indication. Our clinical reviews may utilize, but are not limited to, recognized consensus guidelines, the Institute for Clinical and Economic Review (ICER), and compendium such as the National Comprehensive Cancer Network (NCCN Guidelines®) and DRUGDEX®. Elixir monitors FDA updates and safety announcements daily, as well as follows guidance from the Center of Disease Control and Prevention (CDC) and the U.S. Preventive Service Task Force (USPSTF®).

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The Elixir Clinical Steering Committee brings together leaders from across our national pharmacy care company to monitor the drug landscape, provide recommendations on how to address changes, and to ensure our clients and patients are prepared—in advance.

With any new development, we partner with our Pharmacy & Therapeutics (P&T) committee and consult with our best-in-class specialty pharmacy, to provide a balanced perspective on the clinical effectiveness of all available options, the cost impact to our plan sponsors and patients, and the impact on the overall patient experience.

Kel Riley, MD
Chief Medical Officer

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