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Health Plan Insights

February 2019

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Recent FDA Approvals

New Medications

TRADE NAME (generic name)	MANUFACTURER	DOSAGE FORM STRENGTH	INDICATION(S)	APPROVAL DATE
Jeuveau (prabotulinumtoxinA-xvfs)	Evolus Inc.	Injection, 100 units	For the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.	February 1, 2019
Cablivi (caplacizumab-yhdp)	Ablynx N.V.	Injection, 11mg/vial	For the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy.	February 6, 2019
Egaten (triclabendazole)	Novartis Pharmaceuticals Corporation	Tablet, 250 mg	For the treatment of fascioliasis in patients 6 years of age and older.	February 13, 2019
Herceptin Hylecta (trastuzumab; hyaluronidase-oysk)	Genentech, Inc.	Injection, 600 mg/10,000 units	For the treatment of HER2-overexpressing breast cancer.	February 28, 2019

New Combinations and Formulations

TRADE NAME (generic name)	MANUFACTURER	DOSAGE FORM STRENGTH	INDICATION(S)	APPROVAL DATE
Vancomycin (vancomycin)	Xellia Pharmaceuticals	Injection, 500 mg/100 mL, 1 gm/200 mL, 1.5 gm/300 mL, and 2 gm/400 mL	For the treatment of septicemia, infective endocarditis, skin and skin structure infections, bone infections, and lower respiratory tract infections.	February 15, 2019
Lotemax SM (loteprednol etabonate)	Bausch & Lomb Incorporated	Ophthalmic Gel, 0.38%	For the treatment of post-operative inflammation and pain following ocular surgery.	February 22, 2019
Adhansia XR (methylphenidate hydrochloride)	Purdue Pharmaceuticals L.P.	Capsule, 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg	For the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.	February 27, 2019

New Generics

GENERIC NAME	TRADE NAME	DOSAGE FORM	MANUFACTURER(S)	APPROVAL DATE
Levomilnacipran Hydrochloride	**Fetzima**	Capsules	Amneal Pharmceuticals LLC	February 4, 2019

Pipeline

New Medication Pipeline

DRUG NAME	GENERIC NAME	ROUTE	MECHANISM OF ACTION	INDICATION(S)	ANTICIPATED APPROVAL DATE
Zulresso	Brexanolone	Intravenous	GABA Modulators	Postpartum depression	03/19/2019
JZP-110	Solriamfetol	Oral	CNS stimulant	Excessive sleepiness in narcolepsy / obstructive sleep apnea	03/20/2019
Zynquista	Sotagliflozin	Oral	SGLT1 and SGLT2 inhibitor	Diabetes Mellitus	03/22/2019
Duaklir	Aclidinium Bromide; Formoterol	Inhaled	Long-acting beta-2 adrenoreceptor agonist (LABA), long-acting muscarinic antagonist (LAMA)	Chronic obstructive pulmonary disease	03/31/2019
Mayzent	Siponimod	Oral	Sphingosine 1-phosphate (S1P) receptor modulators	Secondary progressive multiple sclerosis Relapsing multiple sclerosis	03/2019
Evenity	Romosozumab	Subcutaneous	Sclerostin inhibitor	Postmenopausal osteoporosis	1Q 2019
RI-002	Intravenous Immune Globulin	Intravenous	Immunoglobulins	Primary immunodeficiency	04/02/2019
KPT-330 (Oral)	Selinexor	Oral	Nuclear export inhibitor	Multiple myeloma Liposarcoma or leiomyosarcoma	04/06/2019
HTX-011	Bupivicaine; Meloxicam	Injectable	Nonsteroidal anti-inflammatory drugs (NSAIDs), amide anesthetic	Post-operative pain	04/30/2019
Dengvaxia	Tetravalent Dengue Vaccine	Injectable	Vaccine	Dengue	05/01/2019
Barhemsys	Amisulpride	Intravenous	Atypical antipsychotic	Postoperative nausea and vomiting	05/05/2019

DRUG NAME	GENERIC NAME	ROUTE	MECHANISM OF ACTION	INDICATION(S)	ANTICIPATED APPROVAL DATE
Quizartinib	Quizartinib	Oral	Receptor tyrosine kinase inhibitor	Acute myeloid leukemia	05/25/2019
Slinda	Drospirenone	Oral	Progestins	Contraception	05/27/2019
NKTR-181	Loxicodegol	Oral	Opioid agonist	Moderate to severe chronic low back pain	05/28/2019
Zolgensma	Onasemnogene Abeparvovec	Intravenous	Gene therapy	Spinal muscular atrophy	05/2019
Vyleesi	Bremelanotide	Injectable	Peptide melanocortin receptor agonist	Female sexual dysfunction	06/23/2019
Edsivo	Celiprolol	Oral	Beta adrenergic blocking agent	Ehlers-Danlos Syndrome	06/25/2019
ABBV-066	Risankizumab	Subcutaneous	Interleukin 23 (IL-23) antagonist	Moderate to severe plaque psoriasis	2Q 2019
DTG + 3TC	Dolutegravir; Lamivudine	Oral	Integrase inhibitor, nucleoside analogue reverse transcriptase inhibitor (NRTI)	HIV-1 infection	2Q 2019
Nasal Glucagon	Glucagon	Inhaled	Glucagon (recombinant)	Diabetes Mellitus	2Q 2019
Scenesse	Afamelanotide	Implant	Alpha-melanocyte stimulating hormone analog	Erythropoietic protoporphyria	2Q 2019
MK-7655A	Cilastatin Sodium; Imipenem; Relebactam	Intravenous	Beta-lactam antibiotic, dehydropeptidase inhibitor, beta-lactamase inhibitor	Complicated intra-abdominal infections, complicated UTI caused by certain organisms	07/16/2019
Vyndaqel	Tafamidis	Oral	Transthyretin dissociation inhibitor	Transthyretin mediated amyloidosis	07/2019 and 11/2019 (different formulations)
PLX3397	Pexidartinib	Oral	Tyrosine kinase inhibitor	Pigmented villonodular synovitis	08/03/2019
RG6268	Entrectinib	Oral	Tyrosine kinase inhibitor	Solid tumors Solid tumors Non-small cell lung cancer (NSCLC)	08/18/2019

DRUG NAME	GENERIC NAME	ROUTE	MECHANISM OF ACTION	INDICATION(S)	ANTICIPATED APPROVAL DATE
DCDS4501A	Polatuzumab Vedotin	Intravenous	Cytotoxic agent Anti-CD79 antibody	Diffuse large B cell lymphoma	08/19/2019
SRP-4053	Golodirsen	Intravenous	Antisense oligonucleotide	Duchenne muscular dystrophy	08/19/2019
Feraccru	Ferric Maltol	Oral	Iron supplement	Iron deficiency	08/2019
ITI-007	Lumateperone	Oral	5-HT2A serotonin receptor agonist, dopamine D2 receptor agonist, serotonin reuptake inhibitor	Schizophrenia	09/27/2019
Tenapanor	Tenapanor	Oral	Sodium-hydrogen exchanger inhibitor	Irritable bowel syndrome with constipation	09/2019
ABT-494	Upadacitinib	Oral	Janus kinase inhibitor	Rheumatoid arthritis	3Q 2019
Erdafitinib	Erdafitinib	Oral	Fibroblast growth factor receptor inhibitor	Urothelial cancer	3Q 2019
G-Pen	Glucagon	Subcutaneous	Glucagon	Diabetes Mellitus	3Q 2019
COL-144	Lasmiditan	Oral Intravenous	Selective 5-HT1 serotonin agonist	Migraine	4Q 2019
Lefamulin	Lefamulin	Oral Intravenous	Pleuromutilin antibiotic	Community-acquired pneumonia	4Q 2019
YKP3089	Cenobamate	Oral	Antiepileptic agent	Partial onset seizures in epilepsy	4Q 2019
Bronchitol	Mannitol	Inhaled	Mucolytic	Cystic fibrosis	2H 2019
Pedmark	Sodium Thiosulfate	Intravenous	Chelating agent	Chemotherapy-induced ototoxicity	2H 2019

2019 New Generic Pipeline

ANTICIPATED LAUNCH DATE	BRAND NAME	GENERIC NAME	BRAND MANUFACTURER	INDICATION(S)	Previous US SALES
3/1/2019	TEKTURNA	Aliskiren Hemifumarate	Noden Pharma; PDL Biopharma	Hypertension	$54M
3/4/2019	EMEND (injection)	Fosaprepitant Dimeglumine	Merck & Co	Nausea or Vomiting: Chemotherapy-induced nausea and vomiting	$339M
3/16/2019	SYMLIN	Pramlintide Acetate	Amylin	Diabetes Mellitus	$52M
3/25/2019	FASLODEX	Fulvestrant	AstraZeneca	Multiple Cancers	$498M
1Q 2019	AZASITE	Azithromycin	Akorn	Bacterial conjunctivitis	$18M
4/23/2019	CETROTIDE	Cetrorelix	EMD Serono; Merck KGaA	Infertility	$50M
Apr-19	VESICARE	Solifenacin Succinate	Astellas	Overactive bladder	$1,018M
2Q 2019	DELZICOL	Mesalamine	Allergan	Ulcerative colitis	$147M
1H 2019	APTENSIO XR	Methylphenidate Hydrochloride	Rhodes	Attention Deficit Hyperactivity Disorder	$19M
1H 2019	FLECTOR	Diclofenac Epolamine	IBSA Institut Biochemique; Pfizer	Acute pain	$127M
1H 2019	MOVIPREP	Ascorbic Acid; Polyethylene Glycol 3350; Potassium Chloride; Sodium Ascorbate; Sodium Chloride; Sodium Sulfate	Salix; Valeant	Bowel cleansing	$38M
1H 2019	NEXIUM 24HR	Esomeprazole Magnesium	AstraZeneca; Pfizer	Gastroesophageal Reflux Disease (GERD) /Heartburn	$21M
1H 2019	NUVARING	Ethinyl Estradiol; Etonogestrel	Organon; Merck & Co	Contraception	$822M
1H 2019	REMODULIN	Treprostinil	United Therapeutics	Pulmonary Arterial Hypertension	$671M

ANTICIPATED LAUNCH DATE	BRAND NAME	GENERIC NAME	BRAND MANUFACTURER	INDICATION(S)	Previous US SALES
1H 2019	VIVLODEX	Meloxicam	Iroko; iCeutica	Osteoarthritis pain	$24M
1H 2019	ZYTIGA (500 mg)	Abiraterone Acetate	Janssen	Prostate cancer	$88M
7/1/2019	LYRICA (capsules and solution)	Pregabalin	Pfizer	Seizures, neuropathic pain, fibromyalgia	$4,912M
7/19/2019	RELISTOR (tablet)	Methylnaltrexone Bromide	Salix; Valeant; Progenics	Opioid-induced constipation	$44M
Jul-19	FIRAZYR	Icatibant Acetate	Shire; Takeda	Acute attacks of hereditary angioedema	$313M
8/1/2019	THALOMID	Thalidomide	Celgene	Multiple Myeloma, leprosy	$38M
3Q 2019	FORTEO	Teriparatide Recombinant Human	Eli Lilly	Osteoporosis	$940M
10/2/2019	CYSTARAN	Cysteamine Hydrochloride	Leadiant Biosciences	Corneal cystine crystal accumulation in patients with cystinosis	$15M
10/6/2019	JADENU	Deferasirox	Novartis	Treatment of chronic iron overload, non-transfusion-dependent thalassemia	$432M
11/16/2019	OSMOPREP	Sodium Phosphate, Dibasic, Anhydrous; Sodium Phosphate, Monobasic, Monohydrate	Salix; Valeant; Bausch Health	Bowel cleansing	$10M
11/17/2019	ENDOMETRIN	Progesterone	Ferring	Infertility	$44M
11/30/2019	VELETRI	Epoprostenol Sodium	Actelion; Janssen	Pulmonary Arterial Hypertension	$13M
4Q 2019	AFINITOR (2.5 mg, 5 mg, 7.5 mg)	Everolimus	Novartis	Multiple cancer indications	$331M

ANTICIPATED LAUNCH DATE	BRAND NAME	GENERIC NAME	BRAND MANUFACTURER	INDICATION(S)	Previous US SALES
4Q 2019	ZOHYDRO ER	Hydrocodone Bitartrate	Pernix Therapeutics	Severe pain	$38M
2H 2019	INOMAX	Nitric Oxide	INO Therapeutics; Mallinckrodt; Ikaria	Hypoxic respiratory failure in neonates	$474M
2019	ADVIL PM (Liqui-Gels)	Diphenhydramine Hydrochloride; Ibuprofen	Pfizer	Relief of occasional sleeplessness associated with minor aches and pains	$22M
2019	APRISO	Mesalamine	Salix; Valeant; Dr. Falk; Bausch Health	Ulcerative colitis	$259M
2019	BYETTA	Exenatide Synthetic	AstraZeneca	Diabetes Mellitus	$244M
2019	CUPRIMINE (250 mg)	Penicillamine	Aton; Valeant; Bausch Health	Cystinuria, Rheumatoid Arthritis, Wilson's disease	$120M
2019	DESONATE	Desonide	Bayer; LEO Pharma; Dow Pharmaceutical Sciences	Atopic dermatitis	$12M
2019	DUREZOL	Difluprednate	Alcon; Novartis	Uveitis	$181M
2019	EVZIO	Naloxone Hydrochloride	Kaléo Pharma	Opioid overdose	$203M
2019	EXJADE	Deferasirox	Novartis	Treatment of chronic iron overload, Non-transfusion-dependent thalassemia	$165M
2019	FENTORA	Fentanyl Citrate	Cephalon; Teva	Breakthrough cancer pain	$109M
2019	LETAIRIS	Ambrisentan	Gilead	Pulmonary Arterial Hypertension	$215M
2019	LOTEMAX (gel)	Loteprednol Etabonate	Bausch + Lomb; Valeant; Bausch Health	Post-operative inflammation and pain following ocular surgery	$114M
2019	LOTEMAX (suspension)	Loteprednol Etabonate	Bausch + Lomb; Valeant; Bausch Health	Pain associated with cyclitis, herpes zoster, acne rosacea, allergic conjunctivitis, iritis,	$85M

ANTICIPATED LAUNCH DATE	BRAND NAME	GENERIC NAME	BRAND MANUFACTURER	INDICATION(S)	Previous US SALES
2019	MOXEZA	Moxifloxacin Hydrochloride	Alcon; Novartis	Bacterial conjunctivitis	$12M
2019	PREPOPIK	Citric Acid; Magnesium Oxide; Sodium Picosulfate	Ferring	Bowel cleansing	$46M
2019	PROVENTIL-HFA	Albuterol Sulfate	3M; Merck & Co	Asthma	$207M
2019	RESTASIS	Cyclosporine	Allergan	Dry eye	$1,769M
2019	ROZEREM	Ramelteon	Takeda	Insomnia	$97M
2019	SAMSCA	Tolvaptan	Otsuka	Hypervolemic and euvolemic hyponatremia	$107M
2019	TARCEVA (100 mg, 150 mg, 25 mg)	Erlotinib Hydrochloride	OSI Pharmaceuticals; Astellas; Genentech	Multiple Cancer indications	$459M
2019	TRAVATAN Z	Travoprost	Alcon; Novartis	Glaucoma or Ocular Hypertension	$544M

Medication with Significant Label Changes

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
Ambien, Ambien CR (zolpidem tartrate)	**5 Warnings and Precautions** **5.1 CNS-Depressant Effects and Next-Day Impairment** ***(additions underlined)*** …Because AMBIEN (CR) can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.
Antara (fenofibrate)	**5 Warnings and Precautions** **5.3 Liver Function** ***(addition/revision underlined)*** Fenofibrate at doses equivalent to 90 mg Antara per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)].
Butisol Sodium (butabarbital sodium)	**5 Warnings and Precautions** **Warnings** ***(additions underlined)*** …Because BUTISOL SODIUM® (butabarbital sodium tablets, USP and butabarbital sodium oral solution, USP) can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at a higher risk of falls.
Bydureon (exenatide synthetic); **Bydureon Bcise** (exenatide)	**5 Warnings and Precautions** **5.4 Acute Kidney Injury** *(Additions and/or revisions are underlined)* BYDUREON may induce nausea and vomiting with transient hypovolemia and may worsen renal function...Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including BYDUREON. BYDUREON is not recommended for use in patients with an eGFR below 45mL/min/1.73m^2. **5.9 Acute Gallbladder Disease** *(Additions and/or revisions are underlined)* Acute events of gallbladder disease have been reported in GLP-1 receptor agonist trials. In the EXSCEL trial, 1.9% of BYDUREON-treated patients and 1.4% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.
Camtosar (irinotecan hydrochloride)	**5 Warnings and Precautions** **5.2 Myelosuppression** *(Additions and/or revisions are underlined)* CAMPTOSAR can cause severe myelosuppression. Bacterial, viral, and fungal infections have occurred in patients treated with CAMPTOSAR.
Cellcept (mycophenolate mofetil)	**5 Warnings and Precautions** **5.2 Lymphoma and Other Malignancies** *Additions and/or revisions underlined:* … in controlled clinical trials of kidney, heart and liver transplant patients. The majority of PTLD cases appear to be related to Epstein Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children. In pediatric … *Addition of the following two subsections:* **5.12 Effect of Concomitant Medications on Mycophenolic Acid Concentrations**

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
	A variety of drugs have potential to alter systemic MPA exposure when co-administered with CELLCEPT. Therefore, determination of MPA concentrations in plasma before and after making any changes to immunosuppressive therapy, or when adding or discontinuing concomitant medications, may be appropriate to ensure MPA concentrations remain stable. **5.13 Potential Impairment of Ability to Drive of Operate Machinery** CELLCEPT may impact the ability to drive and use machines. Patients should avoid driving or using machines if they experience somnolence, confusion, dizziness, tremor, or hypotension during treatment with CELLCEPT.
Cimzia (certolizumab pegol)	**5 Warnings and Precautions** *Additions and/or revisions underlined:* **5.2 Malignancies** … Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blockers, including CIMZIA. **5.4 Hypersensitivity Reactions** *Newly added information:* The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex which may cause an allergic reaction in individuals sensitive to latex.
Cinvanti (aprepitant)	**5 Warnings and Precautions** **5.2 Hypersensitivity Reactions** *Additions and/or revisions underlined:* Serious hypersensitivity reactions, including anaphylaxis, during or soon after administration of CINVANTI have occurred. Symptoms including dyspnea, eye swelling, flushing, pruritus and wheezing have been reported. Monitor patients during and after administration. If hypersensitivity reactions occur, discontinue CINVANTI and administer appropriate medical therapy. Do not reinitiate CINVANTI in patients who experience these symptoms with previous use.
Cisplatin (cisplatin)	**4 Contraindications** **4 CONTRAINDICATIONS** *(Physician Labeling Rule (PLR) Conversion)* Cisplatin for injection is contraindicated in patients with severe hypersensitivity to cisplatin. **5 Warnings and Precautions** **5.1 Nephrotoxicity** *(Physician Labeling Rule (PLR) Conversion)* Cisplatin for injection can cause dose-related nephrotoxicity, including acute renal failure that becomes more prolonged and severe with repeated courses of the drug. Renal toxicity typically begins during the second week after a dose of cisplatin for injection. Patients with baseline renal impairment, geriatric patients, patients who are taking other nephrotoxic drugs, or patients who are not well hydrated may be more susceptible to nephrotoxicity. Ensure adequate hydration before, during, and after cisplatin for injection administration. Measure serum creatinine, blood urea nitrogen, creatinine clearance, and serum electrolytes including magnesium prior to initiating therapy, and as clinically indicated. Consider magnesium supplementation as clinically needed. Consider alternative treatments or reduce the dose of cisplatin for injection for patients with baseline renal impairment or who develop significant reductions in creatinine clearance during treatment with cisplatin for injection according to clinical treatment guidelines.

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES

5.2 Peripheral Neuropathy

(Physician Labeling Rule (PLR) Conversion)

Cisplatin for injection can cause dose-related peripheral neuropathy that becomes more severe with repeated courses of the drug. Neurologic symptoms have been reported to occur after a single dose. Neuropathy can also have a delayed onset from 3 to 8 weeks after the last dose of cisplatin for injection. Manifestations include paresthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation. The neuropathy may progress further even after stopping treatment. Peripheral neuropathy may be irreversible in some patients.

Perform a neurological examination before initiating cisplatin for injection, at appropriate intervals during therapy, and after completion of therapy. Consider discontinuation of cisplatin for injection for patients who develop symptomatic peripheral neuropathy. Geriatric patients may be more susceptible to peripheral neuropathy.

5.3 Nausea and Vomiting

(Physician Labeling Rule (PLR) Conversion)

Cisplatin for injection is a highly emetogenic antineoplastic agent. Premedicate with anti-emetic agents. Without antiemetic therapy, marked nausea and vomiting occur in almost all patients treated with cisplatin for injection and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 72 hours. Maximal intensity occurs 48 to 72 hours after administration.

Various degrees of vomiting, nausea, and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin for injection therapy. Consider the use of additional anti-emetics following infusion.

5.4 Myelosuppression

(Physician Labeling Rule (PLR) Conversion)

Myelosuppression suppression occurs in 25% to 30% of patients treated with cisplatin for injection. Fever and infection have been reported in patients with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Geriatric patients may be more susceptible to myelosuppression. Perform standard hematologic tests before initiating cisplatin for injection, before each subsequent course, and as clinically indicated. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with cisplatin for injection. For patients who develop severe myelosuppression during treatment with cisplatin for injection, consider dose modifications and manage according to clinical treatment guidelines.

5.5 Hypersensitivity Reactions

(Physician Labeling Rule (PLR) Conversion)

Cisplatin for injection can cause severe hypersensitivity reactions, including anaphylaxis and death. Manifestations have included facial edema, wheezing, tachycardia, and hypotension. Hypersensitivity reactions have occurred within minutes of administration to patients with prior exposure to cisplatin for injection.

Monitor patients receiving cisplatin for injection for possible hypersensitivity reactions. Ensure supportive equipment and medications are available to treat severe hypersensitivity reactions. Severe hypersensitivity reactions require immediate discontinuation of cisplatin for injection and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with cisplatin for injection [see Contraindications (4)]. Cross-reactivity between platinum-based antineoplastic agents has been reported. Cases of severe hypersensitivity reactions have recurred after rechallenging patients with a different platinum agent.

5.6 Ototoxicity

(Physician Labeling Rule (PLR) Conversion)

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
	Cisplatin for injection can cause ototoxicity, which is cumulative and may be severe. Consider audiometric and vestibular function monitoring. Ototoxicity is manifested by tinnitus, hearing loss in the high frequency range (4,000 to 8,000 Hz) and/or decreased ability to hear normal conversational tones. Ototoxicity can occur during or after treatment and can be unilateral or bilateral. Deafness after the initial dose of cisplatin for injection has been reported. Vestibular toxicity has also been reported. Ototoxic effects can be more severe and detrimental in pediatric patients, particularly in patients less than 5 years of age. The prevalence of hearing loss in pediatric patients is estimated to be 40-60%. Additional risk factors for ototoxicity include simultaneous cranial irradiation, treatment with other ototoxic drugs and renal impairment. Consider audiometric and vestibular testing in all pediatric patients receiving cisplatin. Genetic factors (e.g. variants in the thiopurine S-methyltransferase [TPMT] gene) may also contribute to the cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs. **5.7 Ocular Toxicity** *(Physician Labeling Rule (PLR) Conversion)* Optic neuritis, papilledema, and cortical blindness have been reported in patients receiving standard recommended doses of cisplatin for injection. Blurred vision and altered color perception have been reported after the use of regimens with higher doses and dose frequencies of cisplatin for injection. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis and irregular retinal pigmentation of the macular area on fundoscopic exam. Improvement and/or total recovery usually occurs after discontinuing cisplatin for injection but can be delayed. **5.8 Secondary Malignancies** *(Physician Labeling Rule (PLR) Conversion)* The development of acute leukemia secondary to the use of cisplatin for injection has been reported. In these reports, cisplatin for injection was generally given in combination with other leukemogenic agents. **5.9 Embryo-Fetal Toxicity** *(Physician Labeling Rule (PLR) Conversion)* Based on human data, cisplatin for injection can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 14 months after the last dose of cisplatin for injection. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 11 months after the last dose of cisplatin for injection. **5.10 Injection Site Reactions** *(Physician Labeling Rule (PLR) Conversion)* Injection site reactions can occur during the administration of cisplatin for injection. Local soft tissue toxicity has been reported following extravasation of cisplatin for injection. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin for injection solution. Infusion of solutions with a cisplatin for injection concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, necrosis, pain, edema, and erythema. Because of the possibility of extravasation, closely monitor the infusion site during drug administration.
Depacon (valproate sodium)	**Boxed Warning** **WARNING: LIFE THREATENING ADVERSE REACTIONS** *(Additions and/or revisions are underlined)* … **Fetal Risk** **Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores <u>and neurodevelopmental disorders</u> following *in utero* exposure.**

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
	Valproate is therefore contraindicated for prophylaxis of migraine headaches in pregnant women and in women of childbearing potential who are not using effective contraception. Valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise. **5 Warnings and Precautions** **5.2 Structural Birth Defects** *(Subsection title has been revised; additions and/or revisions are underlined)* 5.2 Structural Birth Defects **5.4 Use in Women of Childbearing Potential** *(Additions and/or revisions are underlined)* Because of the risk to the fetus of decreased IQ, neurodevelopmental disorders, and major congenital malformations (including neural tube defects), which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death such as prophylaxis of migraine headaches. Women should use effective contraception while using valproate. Women of childbearing potential should be counseled regularly regarding the relative risks and benefits of valproate use during pregnancy. This is especially important for women planning a pregnancy and for girls at the onset of puberty; alternative therapeutic options should be considered for these patients.
Depakene (valproic acid)	**4 Contraindications** **4 CONTRAINDICATIONS** *(Additions and/or revisions are underlined)* … For use in prophylaxis of migraine headaches: Depakene is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception. **5 Warnings and Precautions** **5.2 Structural Birth Defects** *(Subsection title has been revised; additions and/or revisions are underlined)* 5.2 Structural Birth Defects **5.4 Use in Women of Childbearing Potential** *(Additions and/or revisions are underlined)* Because of the risk to the fetus of decreased IQ, neurodevelopmental disorders, and major congenital malformations (including neural tube defects), which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death such as prophylaxis of migraine headaches. Women should use effective contraception while using valproate. Women of childbearing potential should be counseled regularly regarding the relative risks and benefits of valproate use during pregnancy. This is especially important for women planning a pregnancy and for girls at the onset of puberty; alternative therapeutic options should be considered for these patients.
Depakote, Depakote ER	**Boxed Warning** **WARNING: LIFE THREATENING ADVERSE REACTIONS** *(Additions and/or revisions are underlined)*

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
(divalproex sodium)	**Fetal Risk** **Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores and neurodevelopmental disorders following *in utero* exposure.** **Valproate is therefore contraindicated for prophylaxis of migraine headaches in pregnant women and in women of childbearing potential who are not using effective contraception. Valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise.** **4 Contraindications** **4 CONTRAINDICATIONS** *(Additions and/or revisions are underlined)* … Depakote is contraindicated in patients with known urea cycle disorders. For use in prophylaxis of migraine headaches: Depakote is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception. **5 Warnings and Precautions** **5.2 Structural Birth Defects** *(Subsection title has been revised; additions and/or revisions are underlined)* **5.2 Structural Birth Defects** **5.4 Use in Women of Childbearing Potential** *(Additions and/or revisions are underlined)* Because of the risk to the fetus of decreased IQ, neurodevelopmental disorders, and major congenital malformations (including neural tube defects), which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death such as prophylaxis of migraine headaches. Women should use effective contraception while using valproate. Women of childbearing potential should be counseled regularly regarding the relative risks and benefits of valproate use during pregnancy. This is especially important for women planning a pregnancy and for girls at the onset of puberty; alternative therapeutic options should be considered for these patients.
Dextrose 5%, Sodium Chloride 0.45% and Potassium Chloride 15 MEQ in Plastic Container	**4 Contraindications** **4 CONTRAINDICATIONS** *(Revised Labeling)* Potassium Chloride in Dextrose and Sodium Chloride Injection is contraindicated in patients with: known hypersensitivity to potassium chloride, dextrose and/or sodium chloride clinically significant hyperkalemia clinically significant hyperglycemia **5 Warnings and Precautions** **5.1 Hypersensitivity Reactions** *(Revised Labeling)* Hypersensitivity and infusion reactions, including anaphylaxis, have been reported with Potassium Chloride in Dextrose and Sodium Chloride Injection. Stop the infusion immediately if signs or symptoms of a hypersensitivity or infusion reaction develops. Appropriate therapeutic countermeasures must be instituted as clinically indicated. **5.2 Hyperkalemia** *(Revised Labeling)*

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES

Potassium-containing solutions, including Potassium Chloride in Dextrose and Sodium Chloride Injection may increase the risk of hyperkalemia. Hyperkalemia can be asymptomatic and manifest only by increased serum potassium concentrations and/or characteristic electrocardiographic (ECG) changes. Cardiac arrhythmias, some fatal, can develop at any time during hyperkalemia.

To avoid life threatening hyperkalemia, do not administer Potassium Chloride in Dextrose and Sodium Chloride Injection as an intravenous push (i.e., intravenous injection manually with a syringe connected to the intravenous access, without quantitative infusion device.

Patients at increased risk of developing hyperkalemia and cardiac arrhythmias include those:

- with severe renal impairment, acute dehydration, extensive tissue injury or burns, and certain cardiac disorders such as congestive heart failure or AV block (especially if they receive digoxin).
- with hyperosmolality, acidosis, or undergoing correction of alkalosis (conditions associated with a shift of potassium from intracellular to extracellular space).
- treated concurrently or recently with agents or products that can cause or increase the risk of hyperkalemia.

Avoid use of Potassium Chloride in Dextrose and Sodium Chloride Injection in patients with, or at risk for, hyperkalemia. If use cannot be avoided, use a product with a low amount of potassium chloride, infuse slowly and monitor serum potassium concentrations and ECGs.

5.3 Hyperglycemia and Hyperosmolar Hyperglycemic State

(Revised Labeling)

The use of dextrose infusions in patients with impaired glucose tolerance may worsen hyperglycemia. Administration of dextrose at a rate exceeding the patient's utilization rate may lead to hyperglycemia, coma, and death.

Hyperglycemia is associated with an increase in serum osmolality, resulting in osmotic diuresis, dehydration and electrolyte losses.

Patients with underlying central nervous system disease and renal impairment who receive dextrose infusions, may be at greater risk of developing hyperosmolar hyperglycemic state.

Monitor blood glucose concentrations and treat hyperglycemia to maintain concentrations within normal limits while administering Potassium Chloride in Dextrose and Sodium Chloride Injection. Insulin may be administered or adjusted to maintain optimal blood glucose concentrations.

5.4 Hyponatremia

(Revised Labeling)

Potassium Chloride in Dextrose and Sodium Chloride Injection is a hypertonic solution. In the body, however, glucose containing fluids can become extremely physiologically hypotonic due to rapid glucose metabolization.

Monitoring of serum sodium is particularly important for hypotonic fluids.

Depending on the tonicity of the solution, the volume and rate of infusion, and depending on a patient's underlying clinical condition and capability to metabolize glucose, intravenous administration of glucose can cause electrolyte disturbances, most importantly hypo- or hyperosmotic hyponatremia.

The risk for hyponatremia is increased, in pediatric patients, elderly patients, postoperative patients, those with psychogenic polydipsia and in patients treated with medications that increase the risk of hyponatremia (such as certain diuretic, antiepileptic and psychotropic medications). Close clinical monitoring may be warranted.

Acute hyponatremia can lead to acute hyponatremic encephalopathy characterized by headache, nausea, seizures, lethargy and vomiting. Patients with brain edema are at particular risk of severe, irreversible and life-threatening brain injury. Patients at increased risk for developing complications of hyponatremia, such as hyponatremic encephalopathy include pediatric patients; women, in particular, premenopausal women; patients with hypoxemia; and in patients with underlying central nervous system disease.

Avoid solutions with less than 0.9% Sodium Chloride in patients with or at risk for hyponatremia. If use cannot be avoided, monitor serum sodium concentrations.

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
	Rapid correction of hyponatremia is potentially dangerous with risk of serious neurologic complications such as osmotic demyelination syndrome with risk of seizures and cerebral edema. To avoid complications, monitor serum sodium and chloride concentrations, fluid status, acid-base balance, and signs of neurologic complications. High volume infusion must be used with close monitoring in patients with cardiac or pulmonary failure, and in patients with non-osmotic vasopressin release (including SIADH), due to the risk of hospital-acquired hyponatremia. **5.5 Hypernatremia and Hyperchloremia** *(Revised Labeling)* Electrolyte imbalances such as hypernatremia and hyperchloremia, leading to metabolic acidosis may occur with solutions containing 0.9% Sodium Chloride. Conditions that may increase the risk of hypernatremia, fluid overload and edema (central and peripheral), include patients with pre-eclampsia, primary hyperaldosteronism and secondary hyperaldosteronism associated with, for example, hypertension, congestive heart failure, severe renal insufficiency, liver disease (including cirrhosis), and renal disease (including renal artery stenosis, nephrosclerosis). Medications such as corticosteroids or corticotropin, may increase the risk of sodium and fluid retention. Avoid in patients with or at risk for hypernatremia. If use cannot be avoided, monitor serum sodium concentrations. Rapid correction of hypernatremia is potentially dangerous with risk of serious neurologic complications. Excessively rapid correction of hypernatremia is also associated with a risk for serious neurologic complications such as osmotic demyelination syndrome (ODS) with risk of seizures and cerebral edema. **5.6 Fluid Overload** *(Revised Labeling)* Depending on the volume and rate of infusion, the patient's underlying clinical condition and capability to metabolize dextrose, intravenous administration of Potassium Chloride in Dextrose and Sodium Chloride Injection can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. Avoid Potassium Chloride in Dextrose and Sodium Chloride Injection in patients with or at risk for fluid and/or solute overloading. If use cannot be avoided, monitor fluid balance, electrolyte concentrations, and acid-base balance as needed and especially during prolonged use. **5.7 Refeeding Syndrome** *(Revised Labeling)* Refeeding severely undernourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus, and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. To prevent these complications, monitor severely undernourished patients and slowly increasing nutrient intake.
Diflucan (fluconazole)	**5 Warnings and Precautions** **PRECAUTIONS** **General** ***(additions underlined)*** … <u>Adrenal insufficiency has been reported in patients receiving azoles, including fluconazole.</u> <u>Reversible cases of adrenal insufficiency have been reported in patients receiving fluconazole.</u>
Doral (quezepam)	**5 Warnings and Precautions** **5.2 CNS-Depresant Effects and Daytime Impairment** ***(additions underlined)***

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
	… Because DORAL can cause drowsiness and a decreased level of consciousness, patients particularly the elderly, are at higher risk of falls.
Edluar (zolpidem tartrate)	**5 Warnings and Precautions** **5.1 CNS Depressant Effects and Next-Day Impairment** ***(additions underlined)*** … Because Edluar can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.
Eligard (leuprolide acetate)	**5 Warnings and Precautions** **5.6 Embryo-Fetal Toxicity** *(Newly Added Subsection)* Based on findings in animal studies and mechanism of action, leuprolide acetate may cause fetal harm when administered to a pregnant woman. In animal developmental and reproductive studies, major fetal abnormalities were observed after administration of leuprolide acetate throughout gestation in rats. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus.
Farxiga (dapagliflozin propanediol)	**5 Warnings and Precautions** **5.3 Acute Kidney Injury and Impairment in Renal Function** *(Additions and/or revisions are underlined)* … FARXIGA increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating FARXIGA. Renal function should be evaluated prior to initiation of FARXIGA and monitored periodically thereafter. Use of FARXIGA is not recommended when the eGFR is less than 45 mL/min/1.73 m2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2.
Halcion (triazolam)	**5 Warnings and Precautions** **WARNINGS** ***(additions underlined)*** … Because HALCION can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls. … **PRECAUTIONS** ***(additions underlined)*** …Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients.
Intermezzo (zolpidem tartrate)	**5 Warnings and Precautions** **5.1 CNS Depressant Effects and Next-Day Impairment** ***(additions underlined)*** … Because Intermezzo can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at a higher risk of falls.

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
Kisqali Femara Co-Pack (letrozole; ribociclib succinate)	**5 Warnings and Precautions** **5.1 QT Interval Prolongation** *(Additions and/or revisions are underlined)* KISQALI has been shown to prolong the QT interval in a concentration-dependent manner. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4. In MONALEESA-2 and MONALEESA-7, in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor, 6 out of 574 patients (1%) had > 500 ms post-baseline QTcF value, and 28 out of 574 patients (5%) had a > 60 ms increase from baseline in QTcF intervals. These ECG changes were reversible with dose interruption and the majority occurred within the first four weeks of treatment. There were no reported cases of Torsades de Pointes. In MONALEESA-2, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4. KISQALI is not indicated for concomitant use with tamoxifen. Refer to the Full Prescribing Information for KISQALI. **5.2 Hepatobiliary Toxicity** *(Additions and/or revisions are underlined)* In MONALEESA-2 and MONALEESA-7, increases in transaminases were observed, with Grade 3 or 4 increases in ALT (9% versus 1%) and AST (6% versus 2%) reported in the KISQALI plus aromatase inhibitor and placebo arms respectively. Among the patients who had Grade greater than or equal to 3 ALT/AST elevation, the median time-to-onset was 85 days for the KISQALI plus aromatase inhibitor treatment group. The median time to resolution to Grade less than or equal to 2 was 23 days in the KISQALI plus aromatase inhibitor treatment group. Concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 4 (1%) patients in MONALEESA-2 and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7. **5.3 Neutropenia** *(Additions and/or revisions are underlined)* In MONALEESA-2 and MONALEESA-7, neutropenia was the most frequently reported adverse reaction (77%) and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 63% of patients receiving KISQALI plus an aromatase inhibitor. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade greater than or equal to 2 neutropenia was 16 days. The median time to resolution of Grade greater than or equal to 3 (to normalization or Grade < 3) was 15 days in the KISQALI plus aromatase inhibitor treatment group. Febrile neutropenia was reported in 2% of patients receiving KISQALI plus an aromatase inhibitor. Treatment discontinuation due to neutropenia was 0.7%.
Kuvan (sapropterin dihydrochloride)	**5 Warnings and Precautions** **5.6 Interaction with Levodopa** *Additions and/or revisions underlined:* Monitor patients who are receiving levodopa for change in neurologic status during treatment with Kuvan.
Lonsurf (tipiracil hydrochloride; trifluridine)	**5 Warnings and Precautions** **5.1 Severe Myelosuppression** *(Additions and/or revisions are underlined)* In the 868 patients who received LONSURF in RECOURSE and TAGS, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%),

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
	thrombocytopenia (5%) and febrile neutropenia (3%). Two patients (0.2%) died due to neutropenic infection/sepsis and four other patients (0.5%) died due to septic shock. A total of 12% of LONSURF-treated patients received granulocyte-colony stimulating factors. Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for severe myelosuppression and resume at the next lower dosage. **5.2 Embryo-Fetal Toxicity** *(Additions and/or revisions are underlined)* Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dosage levels resulting in exposures lower than those achieved at the recommended dosage of 35 mg/m2 twice daily. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with LONSURF and for at least 6 months after the final dose.
Lunesta (eszopiclone)	**5 Warnings and Precautions** **5.1 CNS Depressant Effects and Next-Day Impairment** ***(additions underlined)*** … Because Lunesta can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.
Noxafil (posaconazole)	**5 Warnings and Precautions** **5.3 Electrolyte Disturbances** *(Newly added subsection)* Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.
Opdivo (nivolumab)	**5 Warnings and Precautions** *Newly added subsection:* **5.12 Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analog and Dexamethasone** In randomized clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including OPDIVO, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.
Renagel (sevelamer hydrochloride)	**5 Warnings and Precautions** **5.1 Gastrointestinal Adverse Events** *(Additions and/or revisions are underlined)* Dysphagia and esophageal tablet retention have been reported in association with use of sevelamer tablets, some requiring hospitalization and intervention. Consider using sevelamer suspension in patients with a history of swallowing disorders. Cases of bowel obstruction and perforation have also been reported with sevelamer use.
Restoril	**5 Warnings and Precautions** **WARNINGS**

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
(temazepam)	***(additions underlined)*** … Because Restoril can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls. … **PRECAUTIONS** ***(additions underlined)*** … Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients.
Ringers's in Plastic Container (cakcium chloride; potassium chloride; sodium chloride)	**4 Contraindications** **CONTRAINDICATIONS** *(Additions and/or revisions are underlined)* Ringer's Injection is contraindicated in: Patients with known hypersensitivity to the product or any ingredients in the formulation (see **WARNINGS)**. Newborns (less than or equal to 28 days of age) receiving concomitant treatment with ceftriaxone, even if separate infusion lines are used due to the risk of fatal ceftriaxone-calcium salt precipitation in the neonate's bloodstream. **5 Warnings and Precautions** **WARNINGS** *(Additions and/or revisions are underlined)* **Hypersensitivity** Hypersensitivity reactions, including anaphylaxis, have been reported with Ringer's Injection. Stop the infusion immediately if signs or symptoms of a hypersensitivity reaction develop. Appropriate therapeutic countermeasures must be instituted as clinically indicated. **Electrolyte Imbalances** *Hyperkalemia* Potassium-containing solutions, including Ringer's Injection, may increase the risk of hyperkalemia. Patient's at increased risk of developing hyperkalemia include those: ○ With conditions predisposing to hyperkalemia and/or associated with increased sensitivity to potassium, such as patients with severe renal impairment, acute dehydration, extensive tissue injury or burns, certain cardiac disorders such as congestive heart failure ○ Treated concurrently or recently with agents or products that cause or increase the risk of hyperkalemia. Avoid use of Ringer's Injection in patients with, or at risk for, hyperkalemia. If use cannot be avoided, monitor serum potassium concentrations. *Hypernatremia and Hyperchloremia* Electrolyte imbalances such as hypernatremia, hyperchloremia, and metabolic acidosis may occur with Ringer's Injection. Conditions that may increase the risk of hypernatremia, fluid overload and edema (peripheral and/or pulmonary), include patients with aldosteronism; hypertension, congestive heart failure, liver disease, and pre-eclampsia. Certain medications, such as corticosteroids or corticotropin, may also increase risk of sodium and fluid retention.

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
	Avoid Ringer's Injection in patients with, or at risk for, hypernatremia or hyperchloremia. Administration of Ringer's Injection may result in acute kidney injury (AKI) in patients with or at risk for hyperchloremia. If use cannot be avoided, monitor serum sodium and chloride concentrations acid-base balance, and renal function. *Hyponatremia* Ringer's Injection may lead to hyponatremia in at-risk patients. Hyponatremia can lead to acute hyponatremic encephalopathy characterized by headache, nausea, seizures, lethargy, and vomiting. Patients with brain edema are at particular risk of severe, irreversible and life-threatening brain injury. The risk of hospital-acquired hyponatremia is increased in patients with cardiac or pulmonary failure, and in patients with non-osmotic vasopressin release (including SIADH) treated with high volume of hypotonic Ringer's Injection. The risk for hyponatremia is increased in pediatric patients, elderly patients, postoperative patients, those with psychogenic polydipsia, and in patients treated with medications that increase the risk of hyponatremia (such as diuretics, certain antiepileptic and psychotropic medications). Patients at increased risk for developing complications of hyponatremia such as hyponatremic encephalopathy, include pediatric patients, women (in particular, premenopausal women), patients with hypoxemia, and patients with underlying central nervous system disease. Avoid Ringer's Injection in patients with or at risk for hyponatremia. If use cannot be avoided, monitor serum sodium concentrations. Rapid correction of hyponatremia is potentially dangerous with risk of serious neurologic complications. Brain adaptations reducing risk of cerebral edema make the brain vulnerable to injury when chronic hyponatremia is too rapidly corrected, which is known as osmotic demyelination syndrome (ODS). To avoid complications, monitor serum sodium and chloride concentrations, fluid status, acid-base balance, and signs of neurologic complications. *Fluid Overload* Depending on the volume and rate of infusion, the patient's underlying clinical condition, the intravenous administration of Ringer's Injection can cause electrolyte disturbances such as overhydration and congested states including pulmonary congestion and edema. Avoid Ringer's Injection in patients with or at risk for fluid and/or solute overloading. If use cannot be avoided, monitor fluid balance, electrolyte concentrations and acid base balance, as needed and especially during prolonged use. *Hypercalcemia* Ringer's Injection may cause hypercalcemia. Avoid intravenous administration of Ringer's Injection in patients with: hypercalcemia or conditions predisposing to hypercalcemia; and in patients with calcium renal calculi or a history of such calculi.
Soliqua 100/33 (insulin glargine; lixisenatide)	**5 Warnings and Precautions** **5.4 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen** *Additions and/or revisions underlined:*

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
	… When converting from basal insulin therapy or a GLP-1 receptor agonist to SOLIQUA 100/33 follow dosing recommendations.
Sonata (zaleplon)	**5 Warnings and Precautions** **WARNINGS** **Abnormal Thinking and Behavioral Changes** ***(additions underlined)*** … Because Sonata can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.
Trokendi XR (topiramate)	**5 Warnings and Precautions** **5.8 Fetal Toxicity** *(Additions and/or revisions are underlined)* TROKENDI XR can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts) and for being small for gestational age. When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring.
Uloric (febuxostat)	**5 Warnings and Precautions** **5.1 Cardiovascular Death** *(Newly added subsection)* In a cardiovascular (CV) outcome study (ClinicalTrials.gov identifier NCT01101035), gout patients with established CV disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol. The CV outcomes study in patients with gout (CARES) was a randomized, double-blinded, allopurinol-controlled, non-inferiority study conducted to evaluate the risk of major adverse cardiovascular events (MACE) in patients with gout who were treated with ULORIC. The study enrolled patients who had a history of major CV disease, cerebrovascular disease or diabetes mellitus with micro- and/or macrovascular disease. The primary endpoint was the time to first occurrence of MACE defined as the composite of CV death, nonfatal MI, nonfatal stroke, or unstable angina with urgent coronary revascularization. The study was designed to exclude a prespecified risk margin of 1.3 for the hazard ratio of MACE. Results showed that ULORIC was non-inferior to allopurinol for the primary endpoint of MACE [Hazard Ratio: 1.03, 95% Confidence Interval (CI): 0.89, 1.21]. However, there was a significant increase in CV deaths in patients treated with ULORIC (134 [1.5 per 100 patient-years]) compared to patients treated with allopurinol (100 [1.1 per 100 patient-years]) [Hazard Ratio: 1.34, 95% CI: 1.03, 1.73]. Sudden cardiac death was the most common cause of adjudicated CV deaths in the ULORIC group (83 of 3,098; 2.7%) as compared to the allopurinol group (56 of 3,092; 1.8%). ULORIC was similar to allopurinol for nonfatal MI, nonfatal stroke and unstable angina with urgent coronary revascularization . Because of the increased risk of CV death, ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC. Consider use of prophylactic low-dose aspirin therapy in patients with a history of CV disease. Physicians and patients should remain alert for the development of adverse CV event signs and symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
Vantas (histrelin acetate)	**5 Warnings and Precautions** **5.7 Effect on QT/QTc Interval** *(Newly Added Subsection)* Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.
Vemlidy (tenofovir alafenamide)	**5 Warnings and Precautions** **5.3 New Onset or Worsening Renal Impairment** ***(additions and revisions underlined)*** … Prior to or when initiating VEMLIDY, and during treatment with VEMLIDY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue VEMLIDY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.
Xigduo XR (dapagliflozin propanediol; metformin hydrochloride)	**Boxed Warning** **WARNING: LACTIC ACIDOSIS** *(Subsection title has been revised)* ○ **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin- associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin- associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL.** ○ **Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.** ○ **Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information.** **If metformin-associated lactic acidosis is suspected, immediately discontinue XIGDUO XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.** **4 Contraindications** **4 CONTRAINDICATIONS** *(Additions and/or revisions are underlined)* XIGDUO XR is contraindicated in patients with: Severe renal impairment (eGFR below 30 mL/min/1.73 m2), end stage renal disease or patients on dialysis. … **5 Warnings and Precautions** **5.4 Acute Kidney Injury and Impairment in Renal Function** *(Additions and/or revisions are underlined)*

TRADE NAME (generic name)	SUMMARY OF LABEL CHANGES
	Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating XIGDUO XR. Renal function should be evaluated prior to initiation of XIGDUO XR and monitored periodically thereafter. Use of XIGDUO XR is not recommended when the eGFR is less than 45 mL/min/1.73 m2.
Xultophy 100/3.6 (insulin degludec; liraglutide)	**4 Contraindications** *Additions and/or revisions underlined:* In patients with hypersensitivity to XULTOPHY 100/3.6, either insulin degludec or liraglutide, or any of its excipients. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with liraglutide, one of the components of XULTOPHY 100/3.6. **5 Warnings and Precautions** *Additions and/or revisions underlined:* **5.2 Pancreatitis** … In glycemic control trials of liraglutide, there have been 13 cases of pancreatitis … Liraglutide, one of the components of XULTOPHY 100/3.6, has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on liraglutide. **5.4 Hyperglycemia or Hypoglycemia with Changes in XULTROPHY 100/3.6 Regimen** When initiating XULTOPHY 100/3.6, follow dosing recommendations … **5.8 Hypersensitivity and Allergic Reactions** … discontinue XULTOPHY 100/3.6; treat promptly per standard of care, and monitor until signs and symptoms resolve. … Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with XULTOPHY 100/3.6. *Addition of the following subsection:* **5.9 Acute Gallbladder Disease** In a cardiovascular outcomes trial (LEADER trial). 3.1% of patients treated with liraglutide, one of the components of XULTOPHY 100/3.6, versus 1.9% of placebo treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. The majority of events required hospitalization or cholecystectomy. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated. **5.11 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist** *Additions and/or revisions underlined:* Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor …
Zolpimist (zolpidem tartrate)	**5 Warnings and Precautions** **5.5 CNS-depressant effects** ***(additions underlined)*** … Because Zolpimist can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.

Treatment Guideline Updates

TITLE	CITATION / LINK
Neuropsychiatric Symptoms of Huntington's Disease Clinical Practice Guidelines (2019)	Anderson K, van Duijn E, Craufurd D, et al. Clinical Management of Neuropsychiatric Symptoms of Huntington Disease: Expert-Based Consensus Guidelines on Agitation, Anxiety, Apathy, Psychosis and Sleep Disorders. *J. Huntington's Dis*. 2018 Nov;7(4):355–356. https://content.iospress.com/articles/journal-of-huntingtons-disease/jhd180293?resultNumber=1&totalResults=2467&start=0&q=guidelines+anderson+neuropsychiatric+&resultsPageSize=10&rows=10
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