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PharmNOTES

Summary about new FDA-approved products,
new indications, first-time generics,
and WHAT IS IN THE PIPELINE.
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NEWS……

Drug Issue	Date	News/Event
Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz™, Xeljanz XR™)	08/28/2019	The FDA has approved new warnings about an increased risk of blood clots and of death with the 10 mg twice daily dose of tofacitinib (Xeljanz™, Xeljanz XR™), which is used in patients with ulcerative colitis. In addition, the approved use of tofacitinib for ulcerative colitis will be limited to certain patients who are not treated effectively or who experience severe side effects with certain other medicines. Recommendations for healthcare professionals: • Discontinue tofacitinib and promptly evaluate patients with symptoms of thrombosis. • Counsel patients about the risks and advise them to seek medical attention immediately if they experience any unusual symptoms such as: sudden shortness of breath, chest pain that worsens with breathing, swelling of a leg or arm, leg pain or tenderness, or red or discolored skin in the painful or swollen leg or arm. • Reserve tofacitinib to treat ulcerative colitis for patients who have failed or do not tolerate tumor necrosis factor (TNF) blockers. • Avoid tofacitinib in patients who may have a higher risk of thrombosis. • When treating ulcerative colitis, use tofacitinib at the lowest effective dose and limit the use of the 10 mg twice daily dosage to the shortest duration needed. • Report side effects involving tofacitinib to the FDA MedWatch program.

NEWS……

Drug Issue	Date	News/Event
Rare occurrence of serious liver injury with use of certain hepatitis C medicines in some patients with advanced liver disease	08/28/2019	The FDA has received reports that the use of Mavyret™ (glecaprevir and pibrentasvir), Zepatier™ (elbasvir and grazoprevir), and Vosevi™ (sofosbuvir, velpatasvir, and voxilaprevir) to treat chronic hepatitis C in patients with moderate to severe liver impairment has resulted in rare cases of worsening liver function or liver failure. Mavyret™, Zepatier™, and Vosevi™ are FDA-approved to treat chronic hepatitis C in patients without liver impairment or with mild liver impairment (Child-Pugh A), as clinical trials have shown that these medicines are well tolerated and highly effective in this patient population. However, they are not indicated for use in patients with moderate to severe liver impairment. Recommendations for healthcare professionals: • Continue to prescribe Mavyret™, Zepatier™, or Vosevi™ as indicated in the prescribing information for patients without liver impairment or with mild liver impairment (Child-Pugh A). • Of note, Mavyret™ and Zepatier™ should not be prescribed in patients with any history of prior hepatic decompensation. Vosevi™ is indicated for patients who have previously failed certain other Hepatitis C Virus treatments and is not recommended in patients with any history of hepatic decompensation unless the benefits outweigh the risk of liver injury, liver failure or death. • Educate patients to be aware that the risk of serious liver injury is rare and to contact a health professional right away if they develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools as these may be signs of liver injury. • report adverse events or side effects related to the use of these products to the FDA MedWatch program. For more information, please visit: https://www.fda.gov/drugs/drug-safety-and-availability

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Turalio™ (pexidartinib) Capsules, for oral use / Daiichi Sankyo	Antineoplastic agent; Kinase inhibitor Note: Orphan drug designation	Treatment of adult patients with symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery **Boxed warning** Hepatotoxicity	08/02/2019	**DOSAGE AND ADMINISTRATION** The recommended dose is 400 mg orally twice daily. Important administration instructions: Administer on an empty stomach, at least 1 hour before or 2 hours after a meal or snack. **DOSAGE FORMS AND STRENGTHS** Capsules: 200 mg **CONTRAINDICATIONS** None. **WARNINGS AND PRECAUTIONS** • Hepatotoxicity: Turalio™ can cause serious and potentially fatal liver injury and is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). • Embryo-fetal toxicity: Can cause fetal harm. **ADVERSE REACTIONS** Most common adverse reactions: increased lactate dehydrogenase, increased aspartate aminotransferase, hair color changes, fatigue, increased alanine aminotransferase, decreased neutrophils, increased cholesterol, increased alkaline phosphatase, decreased lymphocytes, eye edema, decreased hemoglobin, rash, dysgeusia, and decreased phosphate. **DRUG INTERACTIONS** • Hepatotoxic products: Avoid co-administration with other products known to cause hepatotoxicity. • Strong CYP3A inhibitors: Reduce the dose of Turalio™ if concomitant use of strong CYP3A inhibitors cannot be avoided.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Turalio™ (pexidartinib) Capsules, for oral use / Daiichi Sankyo (continuation)	Antineoplastic agent; Kinase inhibitor Note: Orphan drug designation	Treatment of adult patients with symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery **Boxed warning** Hepatotoxicity	08/02/2019	**DRUG INTERACTIONS** (continuation) • Strong CYP3A inducers: Avoid concomitant use of strong CYP3A inducers. • UGT inhibitors: Reduce the dose of Turalio™ if concomitant use of UGT inhibitors cannot be avoided. • Acid reducing agents: Avoid concomitant use of proton pump inhibitors. Use histamine-2 receptor antagonists or antacids if needed. **USE IN SPECIFIC** of reproductive potential prior to the initiation. **POPULATIONS** • **Pregnancy:** Verify pregnancy status in females • **Females and males of reproductive potential:** Advise females of reproductive potential to use effective contraception during treatment and for 1 month after the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the final dose. • **Lactation:** Advise not to breastfeed. • **Pediatric use:** Safety and effectiveness in pediatric patients have not been established. • **Geriatric use:** Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. • **Renal impairment:** Reduce the dose for patients with mild to severe renal impairment.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Pretomanid Tablets, for oral use / TB Alliance	Anti-mycobacterial Note: Orphan drug designation	As part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB) Limitations of use • Pretomanid Tablets are not indicated for patients with: - Drug-sensitive (DS) TB - Latent infection due to Mycobacterium tuberculosis - Extra-pulmonary infection due to Mycobacterium tuberculosis - MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy • Safety and effectiveness of Pretomanid Tablets have not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen	08/14/2019	**DOSAGE AND ADMINISTRATION** Pretomanid tablets must be administered in combination with bedaquiline and linezolid as follows: • Pretomanid tablet 200 mg orally once daily for 26 weeks. Tablets must be swallowed whole with water. • Bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg 3 times per week, with at least 48 hours between doses, for 24 weeks for a total of 26 weeks. • Linezolid 1,200 mg daily orally for up to 26 weeks, with dose adjustments for known linezolid toxicities. • The combination regimen must be taken with food. • Doses of the regimen missed for safety reasons can be made up at the end of treatment; doses of linezolid alone missed due to linezolid adverse reactions should not be made up. Pretomanid must be administered only as part of a regimen in combination with bedaquiline and linezolid. **DOSAGE FORMS AND STRENGTHS** Tablets: 200 mg. **CONTRAINDICATIONS** • In patients for whom bedaquiline and/or linezolid is contraindicated **WARNINGS AND PRECAUTIONS** • Hepatotoxicity: Hepatic adverse reactions were reported with the use of the combination regimen. Monitor symptoms and signs and liver-related laboratory tests. Interrupt treatment with the entire regimen if evidence of liver injury occurs.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Pretomanid Tablets, for oral use / TB Alliance (continuation)	Anti-mycobacterial Note: Orphan drug designation	As part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB) Limitations of use • Pretomanid Tablets are not indicated for patients with: - Drug-sensitive (DS) TB - Latent infection due to Mycobacterium tuberculosis - Extra-pulmonary infection due to Mycobacterium tuberculosis - MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy • Safety and effectiveness of Pretomanid Tablets have not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen	08/14/2019	**WARNINGS AND PRECAUTIONS** (continuation) • Myelosuppression: Reported with the use of the combination regimen. Monitor complete blood counts. Decrease or interrupt linezolid dosing if significant myelosuppression develops or worsens. • Peripheral neuropathy and optic neuropathy: Reported with the use of the combination regimen. Monitor visual function. Obtain an ophthalmologic evaluation if there are symptoms of visual impairment. Decrease or interrupt linezolid dosing if neuropathy develops or worsens. • QT prolongation: Reported with the use of the combination regimen. Use with drugs that prolong the QT interval may cause additive QT prolongation. Monitor ECGs. Discontinue the combination regimen if significant ventricular arrhythmia or if the patient develops QTcF interval prolongation of greater than 500 ms. • Reproductive effects: Pretomanid caused testicular atrophy and impaired fertility in male rats. Advise patients of reproductive toxicities seen in animal studies and that the potential effects on human male fertility have not been adequately evaluated. • Lactic acidosis: Reported with the use of the combination regimen. Consider interrupting linezolid or the entire combination regimen if significant lactic acidosis develops. **ADVERSE REACTIONS** Most common adverse reactions: peripheral neuropathy, acne, anemia, nausea, vomiting, headache, increased transaminases, dyspepsia, decreased appetite, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyltransferase, lower respiratory tract infection, hyperamylasemia, hemoptysis, back pain, cough, visual impairment, hypoglycemia, abnormal loss of weight, and diarrhea.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Pretomanid Tablets, for oral use / TB Alliance (continuation)	Anti-mycobacterial Note: Orphan drug designation	As part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB) Limitations of use • Pretomanid Tablets are not indicated for patients with: - Drug-sensitive (DS) TB - Latent infection due to Mycobacterium tuberculosis - Extra-pulmonary infection due to Mycobacterium tuberculosis - MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy • Safety and effectiveness of Pretomanid Tablets have not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen	08/14/2019	**DRUG INTERACTIONS** • Strong or moderate CYP3A4 inducers: Avoid co-administration. • Organic anion transporter-3 (OAT3) substrates: Monitor for OAT3 substrate drug-related adverse reactions and consider dosage reduction for OAT3 substrate drugs, if needed. **USE IN SPECIFIC POPULATIONS** • **Lactation:** Breastfeeding is not recommended. • **Males of reproductive potential:** Reduced fertility and/or testicular toxicity were observed in male rats and mice treated with oral pretomanid. These effects were associated with hormonal changes including decreased serum inhibin B and increased serum follicle stimulating hormone and luteinizing hormone in rodents. Reduced fertility and testicular toxicity cannot be definitively ruled out in male human subjects at this time. • **Pediatric use:** Safety and effectiveness have not been established. • **Geriatric use:** Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Wakix™ (pitolisant) tablets, for oral use / Bioprojet pharma	Histamine-3 (H3) receptor antagonist/inverse agonist	Treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy	08/14/2019	**DOSAGE AND ADMINISTRATION** The recommended dosage range is 17.8 mg to 35.6 mg daily. Titrate dosage as follows: • Week 1: Initiate with 8.9 mg once daily • Week 2: Increase dosage to 17.8 mg once daily • Week 3: May increase to the maximum recommended dosage of 35.6 mg once daily Dose modifications are recommended for patients with hepatic and/or renal impairment: • Moderate hepatic impairment: Initial dosage is 8.9 mg once daily. Titrate to a maximum dosage of 17.8 mg once daily after 14 days. • Moderate and severe impairment: Initial dosage is 8.9 mg once daily. Titrate to maximum dosage of 17.8 mg once daily after 7 day. • End stage renal disease (ESRD): Not recommended . For poor metabolizers of CYP2D6, the maximum recommended dosage is 17.8 mg once daily . **DOSAGE FORMS AND STRENGTHS** Tablets: 4.45 mg and 17.8 mg. **CONTRAINDICATIONS** • Patients with severe hepatic impairment. **WARNINGS AND PRECAUTIONS** • QT prolongation: Increases in QT interval. Avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. Monitor patients with hepatic or renal impairment for increased QTc.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Wakix™ (pitolisant) tablets, for oral use / Bioprojet pharma (continuation)	Histamine-3 (H3) receptor antagonist/inverse agonist	Treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy	08/14/2019	**ADVERSE REACTIONS** Most common adverse reactions: insomnia, nausea, and anxiety **DRUG INTERACTIONS** • Strong CYP2D6 inhibitors: Maximum recommended dosage is 17.8 mg once daily. • Strong CYP3A4 inducers: Decreased exposure of Wakix™; consider dosage adjustment. • Sensitive CYP3A4 substrates (including hormonal contraceptives): Wakix™ may reduce effectiveness of sensitive CYP3A4 substrates. Use an alternative non-hormonal contraceptive method during treatment with Wakix™ and for at least 21 days after discontinuation of treatment. **USE IN SPECIFIC POPULATIONS** • **Pregnancy:** There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to Wakix™ during pregnancy. Patients should be encouraged to enroll in the WAKIX pregnancy registry if they become pregnant. • **Pediatric use:** Safety and effectiveness of WAKIX in pediatric patients have not been established • **Hepatic impairment:** Wakix™ is contraindicated in patients with severe hepatic impairment as it has not been studied in this population. Wakix™ is extensively metabolized by the liver and there is a significant increase in exposure in patients with moderate hepatic impairment. Monitor patients with moderate hepatic impairment and adjust the dosage. Monitor patients with mild hepatic impairment. No dosage adjustment is recommended in patients with mild hepatic impairment. • **Renal impairment:** The pharmacokinetics of Wakix™ in patients with end stage renal disease. Therefore, it is not recommended in these patients.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments

Rozlytrek™ (entrectinib) Capsules, for oral use / Genentech, Inc.	Antineoplastic agent; Tyrosine kinase inhibitor	Treatment of:
		• Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive
		• Adult and pediatric patients 12 years of age and older with solid tumors that: (1) have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, (2) are metastatic or where surgical resection is likely to result in severe morbidity, and (3) have progressed following treatment or have no satisfactory alternative therapy
		
		This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
			08/15/2019	**DOSAGE AND ADMINISTRATION**
				The recommended dose for ROS1-Positive NSCLC is 600 mg orally once daily.
				
				The recommended dose for NTRK Gene Fusion-Positive Solid Tumor if:
				• Adults: 600 mg orally once daily
				• Pediatric Patients 12 Years and Older:
				  • BSA greater than 1.50 m2: 600 mg once daily
				  • BSA 1.11 to 1.50 m2 : 500 mg once daily
				  • BSA 0.91 to 1.10 m2 : 400 mg once daily
				
				Patients must be selected based on the presence of ROS1 rearrangement(s) or NTRK gene fusion.
				
				DOSAGE FORMS AND STRENGTHS
				Capsules: 100 mg and 200 mg.
				
				CONTRAINDICATIONS
				None.
				
				WARNINGS AND PRECAUTIONS
				• Congestive heart failure (CHF): Assess left ventricular ejection fraction prior to initiation in patients with symptoms or known risk factors for CHF. Monitor patients for clinical signs and symptoms of CHF. For patients with myocarditis, with or without a decreased ejection fraction, MRI or cardiac biopsy may be required to make the diagnosis. For new onset or worsening CHF, withhold treatment, reassess LVEF and institute appropriate medical management. Reduce dose or permanently discontinue Rozlytrek™ based on severity of CHF or worsening LVEF.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Rozlytrek™ (entrectinib) Capsules, for oral use / Genentech, Inc. (continuation)	Antineoplastic agent; Tyrosine kinase inhibitor	Treatment of: • Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive • Adult and pediatric patients 12 years of age and older with solid tumors that: (1) have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, (2) are metastatic or where surgical resection is likely to result in severe morbidity, and (3) have progressed following treatment or have no satisfactory alternative therapy This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.	08/15/2019	**WARNINGS AND PRECAUTIONS** (continuation) • Central nervous system (CNS) effects: CNS adverse reactions including cognitive impairment, mood disorders, dizziness, and sleep disturbances can occur. Withhold and then resume at same or reduced dose upon improvement or permanently discontinue based on severity. • Skeletal fractures: Rozlytrek™ increases the risk of fractures. Promptly evaluate patients with signs or symptoms of fractures. • Hepatotoxicity: Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue based on severity. If withheld, resume at same or reduced dose based on severity. • Hyperuricemia: Assess serum uric acid levels prior to initiation and periodically during treatment. Monitor patients for signs and symptoms of hyperuricemia. Initiate treatment with urate lowering medications as clinically indicated and withhold for signs and symptoms of hyperuricemia. Resume at same or reduced dose upon improvement based on severity. • QT interval prolongation: Monitor patients who have or who are at risk for QTc interval prolongation. Assess QT interval and electrolytes at baseline and periodically during treatment. Withhold and then resume at same or reduced dose, or permanently discontinue ROZLYTREK based on severity. • Vision disorders: Withhold for new visual changes or changes that interfere with activities of daily living until improvement or stabilization. Conduct an ophthalmological evaluation as appropriate. Resume at same or reduced dose upon improvement or stabilization. • Embryo-fetal toxicity: Can cause fetal harm.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments

Rozlytrek™ (entrectinib) Capsules, for oral use / Genentech, Inc.
 	
(continuation)
	Antineoplastic agent; Tyrosine kinase inhibitor	Treatment of:
		• Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive
		• Adult and pediatric patients 12 years of age and older with solid tumors that: (1) have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, (2) are metastatic or where surgical resection is likely to result in severe morbidity, and (3) have progressed following treatment or have no satisfactory alternative therapy
		
		This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
			08/15/2019	**ADVERSE REACTIONS**
				Most common adverse reactions: fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders.
				
				DRUG INTERACTIONS
				• Moderate and strong CYP3A inhibitors:
				  • For adult and pediatric patients 12 years and older with a BSA greater than 1.50 m2 , reduce the dose of Rozlytrek™ if co-administration cannot be avoided.
				  • For pediatric patients 12 years and older with a BSA less than or equal to 1.50 m2 , avoid co-administration.
				• Moderate and strong CYP3A inducers: Avoid co-administration.
				
				USE IN SPECIFIC POPULATIONS
				• **Pregnancy:** Can cause fetal harm. Verify the pregnancy status of females of reproductive potential prior to initiating .
				• **Females and males of reproductive potential:** Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 weeks following the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months following the final dose.
				• **Lactation:** Advise not to breastfeed.
				• **Renal impairment:** No dose adjustment is recommended for patients with mild or moderate renal impairment. Rozlytrek™ has not been studied in patients with severe renal impairment.
				• **Hepatic impairment:** No dose adjustment is recommended for patients with mild hepatic impairment. Rozlytrek™ has not been studied in patients with moderate and severe hepatic impairment

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Inrebic™ (fedratinib) Capsules, for oral use / Celgene Corporation	Antineoplastic agent; JAK2 inhibitor	Treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis **Boxed warning** Encephalopathy including Wernicke's	08/16/2019	**DOSAGE AND ADMINISTRATION** The recommended dose is 400 mg orally once daily with or without food for patients with a baseline platelet count of greater than or equal to 50 x 109/L. When administering with strong CYP3A4 inhibitors, the dose must be reduced to 200 mg once daily. If co-administration with a strong CYP3A4 inhibitor is discontinued, Inrebic™ dosage should be increased to 300 mg once daily during the first two weeks after discontinuation of the CYP3A4 inhibitor, and then to 400 mg once daily thereafter as tolerated. In patients with severe renal impairment, the dose must be reduced to 200 mg once daily. Conduct baseline testing of thiamine (Vitamin B1) levels prior to initiation. **DOSAGE FORMS AND STRENGTHS** Capsules: 100 mg. **CONTRAINDICATIONS** None. **WARNINGS AND PRECAUTIONS** • Anemia and thrombocytopenia: Manage by dose reduction, interruption, or transfusion. • Gastrointestinal toxicity: Manage by dose reduction or interruption if patient develops severe diarrhea, nausea, or vomiting. Prophylaxis with anti-emetics and treatment with anti-diarrhea medications are recommended. • Hepatic toxicity: Manage by dose reduction or interruption. • Amylase and lipase elevation: Manage by dose reduction or interruption.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Inrebic™ (fedratinib) Capsules, for oral use / Celgene Corporation (continuation)	Antineoplastic agent; JAK2 inhibitor	Treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis **Boxed warning** Encephalopathy including Wernicke's	08/16/2019	**ADVERSE REACTIONS** Most common adverse reactions: diarrhea, nausea, anemia, and vomiting. **DRUG INTERACTIONS** • Strong CYP3A4 inhibitors: Reduce Inrebic™ dose as recommended. • Strong and moderate CYP3A4 inducers: Avoid use of Inrebic™. • Dual CYP3A4 and CYP2C19 inhibitor: Avoid use of Inrebic™. **USE IN SPECIFIC POPULATIONS** • **Lactation:** Advise not to breastfeed. • **Pediatric use:** Safety and effectiveness have not been established. • **Renal impairment:** Reduce Inrebic™ dose when administered to patients with severe renal impairment. No modification of the starting dose is recommended for patients with mild to moderate renal impairment. Due to potential increase of exposure, patients with pre-existing moderate renal impairment require more intensive safety monitoring, and if necessary, dose modifications based on adverse reactions • **Hepatic impairment:** Inrebic™ pharmacokinetics has not been evaluated in patients with severe hepatic impairment. Avoid use in patients with severe hepatic impairment.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Rinvoq™ (upadacitinib) Extended-Release Tablets, for oral use / AbbVie Inc.	Anti-rheumatic; JAK inhibitor	Treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate **Boxed warning** Serious infections, malignancy, and thrombosis	08/16/2019	**DOSAGE AND ADMINISTRATION** The recommended dose is 15 mg once daily. Rinvoq™ may be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs. Avoid initiation or interrupt Rinvoq™ if absolute lymphocyte count is less than 500 cells/mm3 , absolute neutrophil count is less than 1000 cells/mm3 , or hemoglobin level is less than 8 g/dL. **DOSAGE FORMS AND STRENGTHS** Extended-release tablets: 15 mg. **CONTRAINDICATIONS** None. **WARNINGS AND PRECAUTIONS** • Serious infections: Avoid use in patients with active, serious infection, including localized infections. • Malignancy: Consider the risks and benefits of treatment prior to initiating therapy in patients with a known malignancy. • Thrombosis: Consider the risks and benefits prior to treating patients who may be at increased risk of thrombosis. Promptly evaluate patients with symptoms of thrombosis and treat appropriately. • Gastrointestinal perforations: Use with caution in patients who may be at increased risk. • Laboratory monitoring: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. • Embryo-fetal toxicity: May cause fetal harm based on animal studies. • Vaccinations: Avoid use with live vaccines. **ADVERSE REACTIONS** Most common adverse reactions: upper respiratory tract infections, nausea, cough, and pyrexia.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Rinvoq™ (upadacitinib) Extended-Release Tablets, for oral use / AbbVie Inc. (continuation)	Anti-rheumatic; JAK inhibitor	Treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate **Boxed warning** Serious infections, malignancy, and thrombosis	08/16/2019	**DRUG INTERACTIONS** • Strong CYP3A4 inhibitors: Rinvoq™ should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors (e.g., ketoconazole). • Strong CYP3A4 inducers: Co-administration of Rinvoq™ with strong CYP3A4 inducers (e.g., rifampin) is not recommended. **USE IN SPECIFIC POPULATIONS** • **Pregnancy:** May cause fetal harm. Verify the pregnancy status of • females of reproductive potential prior to starting treatment. • **Females of reproductive potential:** Advise female patients of reproductive potential to use effective contraception during treatment and for 4 weeks after the final dose. • **Lactation:** Advise not to breastfeed. • **Pediatric use:** Safety and effectiveness have not been established. • **Renal impairment:** No dose adjustment is required in patients with mild, moderate or severe renal impairment. Use has not been studied in patients with end stage renal disease. • **Hepatic impairment:** No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Not recommended for use in patients with severe hepatic impairment (Child Pugh C).

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Xenleta™ (lefamulin) Tablets and Injection, for oral and intravenous use, respectively / Nabriva Therapeutics plc	Antibacterial	Treatment of adults with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms To reduce the development of drug resistant bacteria and maintain the effectiveness of Xenleta™ and other antibacterial drugs, Xenleta™ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria	08/19/2019	**DOSAGE AND ADMINISTRATION** The recommended dose is: 150 mg every 12 hours by intravenous infusion over 60 minutes, for 5 to 7 days, or 600 mg orally every 12 hours, for 5 days. For patients with severe hepatic impairment (Child-Pugh C), the dose of Xenleta™ injection must be reduced to 150 mg infused over 60 minutes every 24 hours. **DOSAGE FORMS AND STRENGTHS** • Injection: A single-dose clear glass vial containing 150 mg of lefamulin in 15 mL of 0.9% sodium chloride for further dilution. • Tablets: 600 mg of lefamulin. **CONTRAINDICATIONS** • Known hypersensitivity to lefamulin, pleuromutilin class drugs, or any of the components of Xenleta™. • Concomitant use with CYP3A substrates that prolong the QT interval. **WARNINGS AND PRECAUTIONS** • QT prolongation: Avoid use in patients with known QT prolongation, ventricular arrhythmias, and patients receiving drugs that prolong the QT interval such as antiarrhythmic agents. • Embryo-fetal toxicity: May cause fetal harm. • Clostridium difficile-associated diarrhea (CDAD): Evaluate patients who develop diarrhea. **ADVERSE REACTIONS** Most common adverse reactions: • With injection: administration site reactions, hepatic enzyme elevation, nausea, hypokalemia, insomnia, headache. • With tablets: diarrhea, nausea, vomiting, hepatic enzyme elevation.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Xenleta™ (lefamulin) Tablets and Injection, for oral and intravenous use, respectively / Nabriva Therapeutics plc (continuation)	Antibacterial	Treatment of adults with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms To reduce the development of drug resistant bacteria and maintain the effectiveness of Xenleta™ and other antibacterial drugs, Xenleta™ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria	08/19/2019	**DRUG INTERACTIONS** Xenleta™ Injection: • Strong or moderate CYP3A inducers or P-gp inducers: Avoid use unless the benefit outweighs the risk. Monitor for reduced efficacy. Xenleta™ Tablets: • Strong or moderate CYP3A inducers or P-gp inducers: Avoid use unless the benefit outweighs the risk. Monitor for reduced efficacy. • Strong CYP3A inhibitors or P-gp inhibitors: Avoid Xenleta™. • Moderate CYP3A inhibitors or P-gp inhibitors: Monitor for adverse reactions. • CYP3A substrates that prolong the QT interval: Concomitant use is contraindicated. • Midazolam and other sensitive CYP3A substrates: Monitor for adverse reactions. **USE IN SPECIFIC POPULATIONS** • **Pregnancy:** May cause fetal harm. Verify pregnancy status in females of reproductive potential. • **Females of reproductive potential:** Advise females of reproductive potential to use effective contraception during treatment and for 2 days after the final dose. • **Lactation:** A lactating woman should pump and discard human milk for the duration of treatment and for 2 days after the final dose. • **Pediatric use:** Safety and effectiveness have not been established. • **Renal impairment:** No dosage adjustment is warranted. • **Hepatic impairment:** Dosage of Xenleta™ injection should be reduced by extending the dosing interval for patients with severe hepatic impairment. No dosage adjustment of Xenleta™ injection is needed for patients with mild or moderate hepatic impairment. The tablets have not been studied in patients with hepatic impairment. The use of the tablets is not recommended in patients with moderate or severe hepatic impairment.

New FDA Approved Products

Drug/ Manufacturer	Therapeutic Class	Indications	Date	Comments
Nourianz™ (istradefylline), for oral use / Kyowa Kirin, Inc.	Central nervous system agent; Anti-parkinsonian; Adenosine A2A receptor antagonist	As adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "OFF" episodes	08/27/2019	**DOSAGE AND ADMINISTRATION** The recommended dose is 20 mg orally once daily. The dosage may be increased to a maximum of 40 mg once daily. For patients with moderate hepatic impairment, the maximum recommended dose is 20 mg once daily. Use in patients with severe hepatic impairment should be avoided. For patients who smoke 20 or more cigarettes per day (or the equivalent of another tobacco product), the recommended dose is 40 mg once daily. **DOSAGE FORMS AND STRENGTHS** Tablets: 20 mg and 40 mg. **CONTRAINDICATIONS** None. **WARNINGS AND PRECAUTIONS** • Dyskinesia: Monitor patients for dyskinesia or exacerbation of existing dyskinesia. • Hallucinations / psychotic behavior: Consider dosage reduction or stopping if occurs. • Impulse control / compulsive behaviors: Consider dosage reduction or stopping if occurs. **ADVERSE REACTIONS** Most common adverse reactions: dyskinesia, dizziness, constipation, nausea, hallucination, and insomnia.

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Nourianz™ (istradefylline), for oral use / Kyowa Kirin, Inc. (continuation)	Central nervous system agent; Anti-parkinsonian; Adenosine A2A receptor antagonist	As adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "OFF" episodes	08/27/2019	**DRUG INTERACTIONS** • Strong CYP3A4 inhibitors: Recommended maximum dosage with concomitant use is 20 mg once daily. • Strong CYP3A4 inducers: Avoid use. **USE IN SPECIFIC POPULATIONS** • **Pregnancy:** May cause fetal harm. Use during pregnancy is not recommended. • **Females of reproductive potential:** Advise to use contraception during treatment. • **Pediatric use:** Safety and effectiveness have not been established. • **Renal impairment:** No dose adjustment is needed in patients with mild renal impairment, moderate renal impairment, or severe renal impairment. Use has not been evaluated in patients with end-stage renal disease. • **Hepatic impairment:** No dose adjustment is needed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, the steady-state exposures were predicted to be higher than in healthy subjects, based on the estimated mean terminal half-life. Therefore, the maximum recommended dose in patients with moderate hepatic impairment is 20 mg once daily. Closely monitor patients with moderate hepatic impairment for adverse reactions. Use has not been studied in patients with severe hepatic impairment. Avoid use in patients with severe hepatic impairment. • **Tabacco smokers:** Tabacco smoking decreased steady-state systemic exposures, which may decrease efficacy. Therefore, the recommended dose in patients who smoke 20 or more cigarettes per day (or the equivalent amount of another tobacco product) is 40 mg once daily.

New FDA Approved Indications

Drug/ Manufacturer	Therapeutic class	Indications	Date	Comments
Sirturo™ (bedaquiline) Tablets / Janssen Research & Development, LLC	Anti-mycobacterial	**Previous indication(s):** Treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB) **Patient population altered:** As part of combination therapy in pediatric patients over the age of 12 and younger than 18 and weighing at least 66 pounds (30 kilograms) with pulmonary MDR-TB), when an effective treatment regimen cannot otherwise be provided	08/09/2019	-
Myobloc™ (rimabotulinumtoxin B) Injection / Solstice Neurosciences, LLC	Neuromuscular agent; Acetylcholine release inhibitor	**Previous indication(s):** Treatment of cervical dystonia **New indication:** Treatment of chronic sialorrhea	08/20/2019	This approval was supported by several clinical trials. The co-primary efficacy endpoints, measured by decreases in salivary production and improvements in symptoms from baseline, were successfully achieved and statistically significant versus placebo.
Taltz™ (ixekizumab) Injection / Eli Lilly and Company	Interleukin-17A antagonist	**Previous indication(s):** Treatment of plaque psoriasis, psoriatic arthritis **New indication:** Treatment of ankylosing spondylitis (AS)	08/23/2019	This is the third indication for Taltz™. The efficacy and safety of Taltz™ in AS was demonstrated in two studies. In both studies, the primary efficacy endpoint was the proportion of patients at 16 weeks achieving Assessment of Spondyloarthritis International Society 40 (ASAS40) response compared to placebo, which measures disease signs and symptoms such as pain, inflammation and function. Results from both studies demonstrated that patients treated with Taltz™ achieved statistically significant and clinically meaningful improvements in signs and symptoms, as defined by ASAS40 response, compared to placebo.

New FDA Approved Formulations, Dosage Forms, Combination Products and Other Differences

Drug/ Manufacturer	Therapeutic class	Indications	Date	Comments
Eylea™ (aflibercept) Injection / Regeneron Pharmaceuticals, Inc.	Ophthalmic agent; Vascular endothelial growth factor (VEGF) inhibitor	Treatment of patients with neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion, diabetic macular edema, and diabetic retinopathy	08/13/2019	The FDA has approved a new formulation of Eylea™ in a 2mg, single-dose, prefilled syringe. This new formulation provides physicians with a new way to administer Eylea™ that requires fewer preparation steps compared to the vials that were already available in the market.
Harvoni™ (ledipasvir and sofosbuvir) oral pellets / Gilead Sciences Inc.	Antiviral; Hepatitis C Agent	Treatment of chronic hepatitis C virus (HCV) in adults and pediatric patients 3 years of age and older: • Genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis • Genotype 1 infection with decompensated cirrhosis, in combination with ribavirin • Genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin.	08/27/2019	Harvoni™ was already available as oral tablets containing 90 mg of ledipasvir and 400 mg of sofosbuvir or 45 mg of ledipasvir and 200 mg of sofosbuvir. The new formulation in oral pellets is intended to be used in pediatric patients aged 3 years or older and will be available containing 45 mg of ledipasvir and 200 mg of sofosbuvir or 33.75 mg of ledipasvir and 150 mg of sofosbuvir. Harvoni™ pellets are not to be chewed. If Harvoni™ pellets are administered with food, sprinkle the pellets on one or more spoonfuls of non-acidic soft food at or below room temperature. Examples of non-acidic foods include pudding, chocolate syrup, mashed potato, and ice cream. Harvoni™ pellets should be taken within 30 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste.

New FDA Approved Formulations, Dosage Forms, Combination Products and Other Differences

Drug/ Manufacturer	Therapeutic class	Indications	Date	Comments
Sovaldi™ (sofosbuvir) oral pellets / Gilead Sciences Inc.	Antiviral; Hepatitis C Agent	Treatment of: • Adult patients with genotype 1, 2, 3 or 4 chronic HCV infection without cirrhosis or with compensated cirrhosis as a component of a combination antiviral treatment regimen • Pediatric patients 3 years of age and older with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin	08/27/2019	Sovaldi™ was already available as oral tablets containing400 mg and 200 mg of sofosbuvir. The new formulation in oral pellets is intended to be used in pediatric patients aged 3 years or older and will be available containing 200 mg and 150 mg of sofosbuvir. Pellets are not to be chewed. If Sovaldi™ pellets are administered with food, sprinkle the pellets on one or more spoonfuls of non-acidic soft food at or below room temperature. Examples of non-acidic foods include pudding, chocolate syrup, mashed potato, and ice cream. Sovaldi™ pellets should be taken within 30 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste.
Riomet ER™ (metformin hydrochloride for extended-release oral suspension) / Sun Pharm Inds LTD	Antidiabetic; Biguanide	As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus	08/29/2019	Metformin was already available in various other formulations, including immediate-release and extended-release tablets and an immediate-release oral solution. Riomet ER™ is the first extended-release oral suspension formulation of metformin.

New First Time Generic Drug Approval

Drug/Manufacturer	Therapeutic Class	Date	Comments
Halcinonide Topical Cream 0.1% / Mylan Pharmaceuticals Inc.	Dermatological agent; Corticosteroid	08/12/2019	Generic for: Halog Cream
Levocarnitine SF Oral Solution 1 gram/10mL / Novitium Pharma LLC	Endocrine and metabolic agent	08/14/2019	Generic for: Carnitor SF
Tafluprost Ophthalmic Solution/Drops 0.0015% / Micro Labs Limited	Ophthalmologic agent; Prostaglandin	08/19/2019	Generic for: Zioptan
Sapropterin Dihydrochloride Oral Powder 100mg/packet and 500mg/packet / Par Pharmaceutical, Inc.	Endocrine and metabolic agent	08/20/2019	Generic for: Kuvan Powder for Oral Solution
Posaconazole Delayed Release Tablets 100 mg / Sinotherapeutics Inc.	Antifungal	08/21/2019	Generic for: Noxafil Tablets
Nitisinone Capsules 2 mg, 5 mg and 10 mg / Novitium Pharma LLC	Endocrine and metabolic agent	08/26/2019	Generic for: Orfadin Capsules

Source: https://www.drugs.com/generic-approvals.html

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Drug/Manufacturer	Date	Indications	Comments	Impact
ET-105 (lamotrigine) / Eton Pharmaceuticals, Inc.	08/01/2019	Treatment for: Seizures	ET-105 is an oral liquid formulation of lamotrigine in development as an adjunct therapy for partial seizures, primary generalized tonic-clonic seizures, and generalized seizures of Lennox-Gastaut syndrome in patients two years of age and older. The FDA accepted the NDA for ET-105.	Moderate
Triheptanoin / Ultragenyx Pharmaceutical Inc.	08/01/2019	Treatment for: Long-Chain Fatty Acid Oxidation Disorders	Triheptanoin is a synthetic triglyceride compound in development for the treatment of long-chain fatty acid oxidation disorders. Ultragenyx submitted a NDA for triheptanoin.	High High
FMX103 (minocycline) Topical Foam / Foamix Pharmaceuticals Ltd.	08/05/2019	Treatment for: Papulopustular Rosacea	FMX103 is a topical minocycline foam formulation in development for the treatment of moderate-to-severe papulopustular rosacea. Foamix submitted a NDA for FMX103.	Moderate
Avapritinib / Blueprint Medicines Corporation	08/072019	Treatment for: Gastrointestinal Stromal Tumor	Avapritinib (formerly known as BLU-285) is a potent and highly selective KIT and PDGFRα inhibitor in development for the treatment of PDGFRα Exon 18 mutant gastrointestinal stromal tumors (GIST) and fourth-line GIST. The FDA accepted the NDA for avapritinib.	High
Clascoterone Cream / Cassiopea SpA	08/20/2019	Treatment for: Acne	Clascoterone cream is a first-in-class topical androgen receptor inhibitor in development for the treatment of acne. Cassiopea submitted a NDA for clascoterone cream.	Moderate

Source: https://www.drugs.com/new-drug-applications.html

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Drug/Manufacturer	Date	Indications	Comments	Impact
Zanubrutinib / BeiGene, Ltd.	08/21/2019	Treatment for: Mantle Cell Lymphoma	Zanubrutinib is a Bruton's tyrosine kinase (BTK) inhibitor in development for the treatment of patients with mantle cell lymphoma (MCL). The FDA accepted the NDA for zanubrutinib.	High

Source: https://www.drugs.com/new-drug-applications.html

References:

- Drugs.com (www.drugs.com)
- Food and Drug Administration (www.fda.gov)
- IBM Micromedex® (www.micromedexsolutions.com)
- Pharmacist Letter (www.pharmacistletter.com)
- P&T Community (www.ptcommunity.com)