



MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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FDA APPROVES FIRST RADIOACTIVE AGENT FOR NEUROENDOCRINE TUMORS (NET)

The Food and Drug Administration (FDA) approved the first peptide receptor radionuclide therapy (PRRT), which delivers radionuclides directly to tumor cells. Lutathera™ (lutetium Lu 177 dotatate) was granted Priority review and Orphan drug status; it is approved to treat adults with somatostatin receptor-positive gastroenteropancreatic NETs (GEP-NETs), including foregut, midgut, and hindgut NET.

NETs originate in neuroendocrine cells of the body. Symptoms, which may or may not be associated with hormonal hypersecretion, are not typically experienced early in the disease course and may mimic other conditions; hence, over 50% of patients have metastatic disease upon diagnosis. Incidence of NETs has risen markedly since the 1970s. It is estimated that over 12,000 people in the United States (US) are diagnosed with a NET each year, most often in the lungs, gastrointestinal (GI) tract, and pancreas.

The usual first-line systemic therapy for somatostatin receptor positive GI NETs include a somatostatin analogue, such as octreotide or lanreotide, to control hormonal secretion and tumor growth. Approval of Lutathera was based, in part, on the pivotal NETTER-1 trial that compared Lutathera plus standard-dose octreotide long-acting release (LAR) to high-dose octreotide LAR alone (control) in 229 patients with midgut metastatic

NETs. At month 20, the study reported a 79% lower risk of disease progression or death with Lutathera compared to control. Median progression-free survival (PFS) was 8.5 months in the control group and had not been reached in the Lutathera group. Overall response rate with Lutathera was 18% compared to 3% with control. The most common grade 3 or 4 adverse events reported more often with Lutathera included lymphopenia and vomiting.

The recommended dose of Lutathera is 7.4 GBq administered intravenously (IV) over 30 minutes every 8 weeks for a total of 4 doses. It is given in conjunction with octreotide LAR 30 mg intramuscular (IM) 4 to 24 hours after each Lutathera dose. Advanced Accelerator Applications is preparing for launch of Lutathera in the US, with delivery directly to hospitals and treatment centers.

AMERICAN COLLEGE OF CARDIOLOGY (ACC) HEART FAILURE (HF) DECISION PATHWAY

The ACC developed an Expert Consensus Decision Pathway to facilitate optimal treatment of patients with reduced ejection fraction (HFrEF); this document is a compliment to the ACC consensus guideline for HF management. The new pathway focuses on pharmacologic treatment of chronic ambulatory HFrEF, and discusses medication initiation and titration, as well as challenges of care. Key recommendations include starting therapy with an angiotensin-converting enzyme inhibitor (ACEI)

or angiotensin II receptor blocker (ARB), if congestion is present, versus an evidence-based beta blocker, in patients with adequate resting HF and less congestion; use of an angiotensin receptor-neprilysin inhibitor (ARNI) after an ACEI or ARB; and addition of ivabradine in select patients in sinus rhythm. HFrEF management in specific populations, such as African American, elderly, and frail patients is also discussed.

The pathway reviews challenges faced with HF management including the high rate of nonadherence (up to 50%) to prescribed multiple medications. While dose titration may increase drug tolerability, studies show that strategies, such as integration of care, mobile healthcare, and patient education regarding their illness and prescribed medications, may improve mortality and decrease hospital admissions. ACC emphasizes that achieving target doses leads to the best HFrEF outcomes. Factors that hinder the use of optimal treatment, including comorbidities, cost of care, and treatment adherence, should be addressed. Finally, care should focus on both the patients' symptoms and functional capacity, as well as improving cardiac function.

■ IV SALINE SOLUTION SHORTAGE

On January 16, 2018, the FDA provided an update on the serious shortage of sodium chloride 0.9% (saline) injection bags currently experienced at healthcare facilities across the US. Saline bags, used for IV drug administration, have been in intermittent short supply since 2014. The impact of Hurricane Maria on Puerto Rico, where many medical products are produced, has greatly worsened this supply dilemma. The Agency also noted that the 2017-2018 flu season has been more severe than typically experienced, resulting in an increase in demand for IV saline fluids and further exacerbation of the shortage.

In an effort to resolve the saline fluid shortage, the FDA is assisting manufacturing facilities in Puerto Rico to operate at full capacity. Other steps taken include temporarily allowing the import of IV saline products from facilities outside the US (e.g., Baxter and B. Braun foreign facilities), encouraging increased production at existing facilities, and expediting the approval process for IV saline products (Fresenius Kabi, Grifols Laboratories).

Manufacturers are allocating IV saline products to providers, based on historical use, until supply improves. The FDA also has received accounts of institutions rationing weakened supply and/or repackaging or compounding IV saline fluids, using empty IV containers, in order to provide the prescribed end-volume to the patient. As a result, the Agency is also monitoring supply of empty IV containers.

■ INJECTABLE VARUBI® HYPERSENSITIVITY ALERT

The FDA is alerting the public of post-marketing reports of serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock (some requiring hospitalization), associated with injectable rolapitant (Varubi). This substance P/neurokinin 1 (NK1) receptor antagonist is indicated to prevent delayed nausea and vomiting associated with cytotoxic chemotherapy. Rolapitant injection is administered IV over 30 minutes within 2 hours before chemotherapy on day 1 of each cycle. Hypersensitivity reactions have occurred during or soon after the infusion, most within the first few minutes of administration. The FDA is advising healthcare professionals (HCPs) to assess patient history of hypersensitivity to any component of the product (including soybean oil) or other allergens that may have cross-reactivity. HCPs must be vigilant for signs of hypersensitivity both during and after the rolapitant infusion. Symptoms of anaphylaxis can include wheezing or difficulty breathing; swelling of the face or throat; hives or flushing; itching; abdominal cramping, abdominal pain, or vomiting; back or chest pain; and hypotension or shock. Anaphylaxis has not been reported with the rolapitant oral tablet formulation.

■ BOXED WARNING REMOVED FOR COMBINATION ASTHMA THERAPY

The FDA concluded that treatment of asthma with long-acting beta agonists (LABA) in combination with inhaled corticosteroids (ICS) does not lead to significantly more serious asthma-related adverse effects than treatment with ICS alone. This determination is based on results of 4 large clinical safety trials with 41,297 asthma patients (1 study included children aged 4 to 11 years) who were treated with combination LABA/ICS therapy for 6 months. Results revealed that the addition of a LABA to ICS therapy does not cause a significant increase in the risk of serious asthma outcomes compared to ICS alone, and that the combination is more effective in reducing asthma attacks. Consequently, the Agency removed the boxed warning for asthma-related death from the labeling of ICS/LABA combination products that are indicated for asthma. Select combination ICS/LABA products are also used to treat chronic obstructive pulmonary disease (COPD). The boxed warning regarding the increase in risk of asthma-related death with use of LABAs alone to treat asthma will remain in the labeling for single-component LABA agents.

DRUG INFORMATION HIGHLIGHTS

- Based on an extensive review and key expert opinion, the FDA determined that the risks of slowed or difficult breathing, misuse, abuse, addiction, overdose, and death associated with opioid-containing cough and cold products outweigh their benefits in patients < 18 years of age; therefore, the Agency is limiting their use to adults only. The FDA is requiring a boxed warning about these risks be added to the product label; other warnings will also be added that are consistent with prescription opioid pain medicines. Alternative cough and cold products for pediatrics include over-the-counter (OTC) dextromethorphan and prescription benzonatate. The Agency is also considering regulatory action of codeine-containing cough and cold products that are available OTC in some states.
- Genentech's vascular endothelial growth factor antibody, bevacizumab (Avastin®), was granted full approval for the treatment of adults with recurrent glioblastoma. This indication was previously approved under the Accelerated approval pathway; conversion to full approval was based on phase 3 trial data that reported an increase in median PFS compared to chemotherapy alone (4.2 versus 1.5 months). There was no difference in overall survival.
- Companion Medical announced the launch of InPen®, a prescription-only, smart insulin pen system. It is indicated for use with Humalog® and Novolog® rapid-acting insulins in patients ≥ 12 years of age. InPen calculates optimal dosing, reminds the user when to dose, monitors insulin temperature, tracks dose history for 1 year, transmits data to a mobile device, displays last dose and remaining amount of insulin, and generates reports for HCPs. It is compatible with iOS and Android systems.
- The first oral poly (ADP-ribose) polymerase (PARP) inhibitor has been approved for the treatment of breast cancer. Under Priority review, olaparib (Lynparza®) tablets received a new indication to treat patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Patients are selected for therapy based on an FDA-approved companion diagnostic for olaparib (e.g., BRACAnalysis CDx™). Recommended tablet dose is 300 mg twice daily, with or without food, until disease progression or unacceptable toxicity occur. This new indication does not apply to olaparib capsules; capsules should not be substituted for the tablets, even on a milligram-per-milligram basis. Olaparib tablet is also indicated for the treatment of select patients with ovarian cancer.
- The FDA added therapy discontinuation recommendations to the labeling of nilotinib (Tasigna®). Discontinuation may be considered after ≥ 3 years of use in patients with Philadelphia-positive chronic myelogenous leukemia in the chronic phase (Ph+ CML-CP) who have achieved a sustained molecular response; patients can either be newly diagnosed or be resistant or intolerant to imatinib. To be considered for discontinuation, patients must have typical BCR-ABL transcripts as detected by an appropriate FDA-authorized test. Continued remission is monitored with repeat testing.

PIPELINE NEWS: UPCOMING PRESCRIPTION DRUG/BIOSIMILAR USER FEE ACT (PDUFA/BsUFA) DATES

- **February-March, 2018:** Imfinzi™; durvalumab; IV programmed death-ligand 1 (PD-L1) blocking antibody; non-small cell lung cancer (NSCLC); AstraZeneca.
- **February-March, 2018:** Latuda®; lurasidone; oral antipsychotic; bipolar disorder (ages 10-17 years); Sumitomo Dainippon.
- **February-March, 2018:** rituximab, biosimilar to Genentech's Rituxan®; rheumatoid arthritis (RA), chronic lymphocytic leukemia, non-Hodgkin's lymphoma, antineutrophil cytoplasmic antibodies-associated vasculitis; Celltrion/Teva.
- **February 12, 2018:** bictegravir/emtricitabine/tenofovir alafenamide; oral fixed-dose antiretroviral; human immunodeficiency virus 1 (HIV-1) infection; Gilead.
- **February 12, 2018:** dexamethasone; intraocular long-acting corticosteroid; ocular inflammation post cataract surgery; Icon.
- **February 14, 2018:** Makena® auto-injector; hydroxyprogesterone caproate; subcutaneous (SC) progestin; preterm birth; AMAG.
- **February 23, 2018:** benzhydrocodone/acetaminophen; oral abuse-deterrent immediate-release opioid-containing analgesic; acute pain; Kempharm.
- **February 28, 2018:** tezacaftor/ivacaftor; oral fixed-dose cystic fibrosis (CF) transmembrane conductance corrector + enhancer; CF; Vertex.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
tofacitinib immediate- and extended-release (IR and ER)	Xeljanz®/ Xeljanz XR	Tofacitinib IR and ER tablets (Xeljanz/Xeljanz XR) received a new indication for the treatment of active psoriatic arthritis (PsA) in adults with an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). The Janus kinase inhibitor is also approved for adults with RA. The recommended dose is 5 mg twice daily (IR) or 11 mg once daily (ER) for both indications.	Pfizer	sNDA approval 12/14/2017
bosutinib	Bosulif®	Bosutinib (Bosulif), a kinase inhibitor, gained Orphan drug status and a new indication for newly-diagnosed Ph+ CML-CP; continued approval may depend upon results of confirmatory trials. The dosage is 400 mg orally, once daily with food. Bosutinib is also indicated for chronic, accelerated, or blast phase Ph+ CML.	Pfizer	sNDA Accelerated Priority approval 12/19/2017
cabozantinib tablet	Cabometyx®	The FDA approved a new indication for the tablet formulation of the kinase inhibitor cabozantinib (Cabometyx) for the treatment of advanced renal cell carcinoma (RCC); use is no longer limited to patients with prior anti-angiogenic therapy. Recommended dose is 60 mg orally once daily. Cabozantinib tablets (20 mg, 40 mg, 60 mg) are not substitutable for cabozantinib capsules (20 mg, 80 mg; Cometriq®), which are approved for medullary thyroid cancer.	Exelixis	sNDA Priority approval 12/19/2017
ertugliflozin; ertugliflozin/sitagliptin; ertugliflozin/metformin	Steglatro™ Steglujan™ Segluromet™	Ertugliflozin (Steglatro), an oral sodium glucose co-transporter 2 (SGLT2) inhibitor, was approved as single-component tablets and in fixed-dosed combinations with sitagliptin (Steglujan) and metformin (Segluromet). All 3 products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Starting dose of Steglatro, approved as 5 mg and 15 mg tablets, is 5 mg daily in the morning, without regard for food. Steglujan, ertugliflozin/sitagliptin, is approved as fixed-dose tablets of 5 mg/100 mg and 15 mg/100 mg; starting dose is 5 mg/100 mg once daily, taken in the morning, without regard for food. Segluromet, ertugliflozin/metformin, is taken twice daily with meals; dosage is based on the current regimen; it is approved in 2.5 mg/500 mg, 2.5 mg/1,000 mg, 7.5 mg/500 mg, and 7.5 mg/1,000 mg strengths.	Merck	NDA approval 12/19/2017
valsartan	Prexxartan®	A 4 mg/mL oral solution of the ARB, valsartan (Prexxartan), was approved to treat hypertension (HTN) in patients ≥ 6 years of age and in patients unable to swallow valsartan tablets with HF (NYHA class II-IV) or with stable left ventricular failure or left ventricular dysfunction following myocardial infarction (MI). Adult dose ranges from 20 mg to 160 mg twice daily; pediatric dose for HTN is 0.65 to 1.35 mg/kg twice daily. Launch is planned in the first half of 2018.	Carmel Biosciences	505(b)(2) NDA approval 12/19/2017

ANDA=Abbreviated New Drug Application; BLA=Biologics License Application; NDA=New Drug Application; sBLA=Supplemental Biologics License Application; sNDA = Supplemental New Drug Application

RECENT FDA APPROVALS *continued*

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
nivolumab	Opdivo®	Breakthrough therapy designation and a broadened indication were granted to the programmed death receptor-1 (PD-1) blocking antibody, nivolumab (Opdivo), to include patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting. The recommended dose is 240 mg every 2 weeks via IV infusion over 60 minutes. Nivolumab is also indicated for several other malignant conditions.	Bristol-Myers Squibb	sBLA approval 12/20/2017
pertuzumab	Perjeta®	The HER2/neu receptor antagonist pertuzumab (Perjeta) was granted a new indication to be used in combination with trastuzumab and docetaxel for adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence. For this indication, it is administered post-operatively every 3 weeks for a total of 1 year (up to 18 cycles). Initial dose is 840 mg via IV infusion, followed by 420 mg infused IV, thereafter. Pertuzumab's indication for neoadjuvant therapy of HER2-positive, locally-advanced, inflammatory, or early stage breast cancer was also converted to full approval.	Genentech	sBLA Priority approval 12/20/2017
angiotensin II	Giapreza™	An IV vasoconstrictor, angiotensin II (Giapreza), has been granted approval to increase blood pressure in adults with septic shock and other distributive shock. Giapreza is approved as 2.5 mg/mL, in 1 mL and 2 mL vials. After further dilution, a weight-based dose is given via IV infusion as instructed in the product label.	La Jolla	NDA Priority approval 12/21/2017
hydroxyurea	Siklos®	Orphan drug status and approval have been awarded to a new formulation of the antimetabolite, hydroxyurea (Siklos), to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients ≥ 2 years of age with sickle cell anemia and recurrent moderate to severe painful crises. Siklos is approved as 100 mg and functionally triple-scored 1,000 mg tablets. The recommended initial dose is 20 mg/kg given orally once daily, which may be increased until a maximum tolerated dose of 35 mg/kg/day is reached, as long as blood counts remain in an acceptable range. Siklos carries boxed warnings for myelosuppression and malignancies.	Medunik	505(b)(2) NDA Priority approval 12/21/2017

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RECENT FDA APPROVALS *continued*

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
brimonidine tartrate	Lumify™	The FDA has given approval for an OTC formulation of the alpha-adrenergic agonist brimonidine (Lumify) for relief of redness of the eye due to minor eye irritations. Dosing for adults and children ≥ 5 years of age is 1 drop in the affected eye(s) every 6 to 8 hours. Lumify is approved as a 2.5 mL 0.025% ophthalmic solution. Lumify is expected to be available in the second quarter of 2018. Prescription strengths of brimonidine, used to treat glaucoma and increased intraocular pressure, are 0.1%, 0.15%, and 0.2%.	Bausch & Lomb	505(b)(2) NDA approval 12/22/2017
cysteamine bitartrate	Procysbi®	Cysteamine bitartrate (Procysbi) received an expanded indication to include children aged ≥ 1 year with nephropathic cystinosis, a life-threatening metabolic lysosomal storage disorder that causes irreversible organ damage. Previously, Procysbi was approved for patients ≥ 2 years of age with the disorder. Dosage is weight-based, given orally every 12 hours. Contents of the delayed-release capsules can be sprinkled on to applesauce or berry jelly and consumed within 30 minutes.	Horizon	sNDA approval 12/22/2017
denosumab	Xgeva®	The FDA expanded the indication for the RANK ligand inhibitor, denosumab (Xgeva), to include prevention of skeletal-related events in patients with multiple myeloma. The dosage for this indication is 120 mg SC every 4 weeks. Xgeva is also approved for prevention of skeletal-related events in patients with metastatic solid tumor, treatment of giant cell tumor of the bone, and treatment of hypercalcemia of malignancy. Notably, denosumab (Prolia®) indications are in the osteoporosis setting and differ from Xgeva.	Amgen	sBLA approval 01/04/2018
afatinib	Gilotrif®	An expanded indication was awarded to afatinib (Gilotrif), a kinase inhibitor, to include first-line treatment of metastatic NSCLC in patients whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test; mutations do not include EGFR exon 19 deletions or exon 21/L858R substitution mutations. Safety and efficacy were not established for use against resistant EGFR mutations. Afatinib is also indicated for squamous NSCLC in select patients. Dosage is 40 mg orally once daily.	Boehringer Ingelheim	sNDA Priority approval 01/12/2018

Select approvals are captured in the table.

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References:

acc.org cdc.gov companionmedical.com fda.gov

BONUS FLU REPORT

The 2017-2018 flu season has been severe and has still not peaked in most areas of the US. This Bonus Flu Report provides highlights of the current flu season.

2017-2018 Influenza Season Update (as of week ending January 27, 2018)

■ KEY FLU INDICATORS:

- In the US, 48 states reported widespread influenza activity.
- High hospitalization rate associated with influenza was reported, with the highest percentage in people \geq 65 years of age, followed by those aged 50-64 years.
- To date, 53 flu-related pediatric deaths have been reported; the Centers for Disease Control and Prevention (CDC) anticipates that more pediatric deaths will occur this season compared to the 2014-2015 season (total pediatric deaths was 148), which had similar virus activity.
- The CDC continues to recommend influenza vaccination for all persons 6 months of age and older, as flu viruses are likely to continue circulating for several more weeks.

■ FLU VACCINE EFFECTIVENESS:

- This season's flu vaccine includes the same influenza A(H3N2) vaccine component as in the 2016-2017 vaccine; most circulating H3N2 viruses tested in the US this season are still similar to the H3N2 vaccine virus.
- For the 2016-2017 season, the overall vaccine effectiveness (VE) against all circulating flu viruses was 39%, and VE against H3N2 viruses was 32%; CDC expects a similar VE for the 2017-2018 season if the same influenza A(H3N2) viruses continue to predominate.
- Of 1,597 influenza-positive specimens reported to the CDC, 79.5% have been influenza H3N2.

■ ANTIVIRAL DRUG SUPPLY:

- The CDC advises that all hospitalized patients and high-risk patients with suspected influenza be treated as soon as possible with oseltamivir (Tamiflu®, generic), zanamivir (Relenza®), or peramivir (Rapivab®).
- According to the CDC, the total national supply of influenza antiviral drugs is expected to be sufficient to meet the high seasonal demand.
- The CDC is aware of delays in filling wholesaler orders and spot shortages in areas of high demand; there is not a nationwide shortage of antivirals.
- Currently, Genentech (brand Tamiflu) and all generic oseltamivir manufacturers (with the exception of Avkare's generic oseltamivir 30 mg capsules) are manufacturing and shipping product. Furthermore, there is no supply shortage of zanamivir (Relenza) or peramivir (Rapivab).
- Product availability is subject to change.

■ RESOURCES:

- ASHP: <https://www.ashp.org/Drug-Shortages/Current-Shortages/>
- CDC: <https://www.cdc.gov/flu/index.htm>
- FDA: <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm100228.htm>