



MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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ICER REPORTS ON SIPONIMOD FOR MS

Multiple sclerosis (MS) affects approximately 400,000 Americans. Several treatments have been approved in the United States (US) for the treatment of relapsing forms of MS, which account for about 85% to 90% of cases and are characterized by clinical episodes of neurologic deficits. However, few treatments are approved specifically for progressive disease courses, described as increasing disability independent of MS relapses. In March 2019, the Food and Drug Administration (FDA) approved Novartis' siponimod (Mayzent™), an oral selective sphingosine-1-phosphate (S1P) modulator similar to fingolimod (Gilenya®; Novartis), for relapsing forms of MS, including active secondary progressive MS (SPMS), which follows an initial relapsing-remitting disease course.

The Institute for Clinical and Economic Review (ICER) evaluated the role of siponimod for SPMS. Their published findings note that siponimod demonstrated effectiveness in relapse reduction, but did not demonstrate improvement in disability progression independent of relapses (non-active SPMS) or worsening ambulation. Likewise, siponimod does not offer a unique role in therapy. ICER did, however, find a high certainty that siponimod provides at least a small net benefit in patients with active SPMS compared to best supportive care.

Regarding long-term cost-effectiveness, ICER assessed oral siponimod as having an incremental cost-effectiveness ratio

of \$433,000 per quality-adjusted life year (QALY) gained in patients with active SPMS compared to best supportive care, exceeding commonly accepted thresholds for cost-effectiveness. ICER evaluated only siponimod's role in active SPMS and did not estimate the budget impact of value-based price benchmarks. They recommended a price decrease for siponimod to better align with its value-add, enlisting patient organizations to demand value-based pricing on new therapies. ICER further stated that payers may prefer fingolimod generics, once launched, over siponimod when evaluating formularies.

BIOSIMILAR CORNER

NEW BIOSIMILARS APPROVED

Amgen's trastuzumab-anns (Kanjinti™), a biosimilar to Genentech's Herceptin™, was FDA-approved for the same indications as the reference product, which include treatment of HER2 overexpressing forms of breast and gastric/gastroesophageal junction cancers. Intravenously (IV) administered Kanjinti is approved as a 420 mg lyophilized powder for reconstitution in a multiple-dose vial (MDV). Bevacizumab-bvzr (Zirabev™), by Pfizer, is a biosimilar to Genentech's Avastin®. It was approved for all indications as the originator product regarding metastatic colorectal cancer, non-squamous non-small cell lung cancer (NSCLC), glioblastoma, renal cell carcinoma, and cervical cancer. Unlike Avastin, Zirabev is not

indicated to treat epithelial ovarian, fallopian tube, or primary peritoneal cancer. Zirabev 25 mg/mL is approved in 4 mL and 16 mL single-dose vials (SDV) to be given via IV infusion. Another biosimilar by Pfizer, rituximab-pvvr (Ruxience™), was FDA-approved; its reference product is Genentech's Rituxan®. Ruxience holds the same indications regarding non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and polyangiitis (granulomatosis and microscopic) as Rituxan but is not approved for rheumatoid arthritis (RA) or pemphigus vulgaris like the originator product. Ruxience 10 mg/mL is approved in 10 mL and 50 mL SDVs for IV infusion. Lastly, Samsung-Bioepis' subcutaneous (SC) adalimumab-bwwd (Hadlima™) was approved as a biosimilar to Abbvie's Humira®. Hadlima was granted the same indications as Humira regarding RA, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease (CD), and ulcerative colitis (UC). Unlike Humira, Hadlima did not garner approval for hidradenitis suppurativa or pediatric CD. In addition, while Hadlima is approved to treat juvenile idiopathic arthritis (JIA) in patients ≥ 4 years of age, the originator is indicated for those ≥ 2 years old with JIA. Hadlima is approved as a 40 mg/0.8 mL single-dose prefilled syringe and autoinjector.

Biosimilars to Janssen's Remicade®, infliximab-abda (Renflexis®; Merck) and infliximab-dyyb (Inflectra®; Pfizer/Celltrion), received expanded UC indications to include patients as young as 6 years of age; previously they were only approved in adults for UC.

No clinically meaningful differences exist between a biosimilar and its originator product. Availability of biosimilars has the potential to increase access to important therapies and lower costs. Launch of Hadlima is expected on or after June 30, 2023. Amgen announced that Kanjinti and bevacizumab-awwb (Mvasi™), its biosimilar version of Avastin approved in 2017, are now available in the US; however, litigation regarding patent protection for each product is ongoing. Launch plans for Zirabev or Ruxience have not been announced.



BEHAVIORAL HEALTH CORNER

ICER'S FINAL REPORT ON ESKETAMINE

Approximately 7% of adults in the US experience ≥ 1 major depressive episode annually, and treatment-resistant depression (TRD) occurs in approximately one-third of these cases. TRD is considered when a patient has an insufficient response to treatment

of adequate dosing and duration, most commonly including ≥ 2 trials of antidepressant monotherapy. In addition to the continued effects of the depressed episode on suicide risk and social relationships, treatment-resistant patients have higher costs of care and decreased work productivity. Moreover, treatments can have a wearing-off effect, and side effects can be cumbersome. In March 2019, the FDA approved Janssen's esketamine (Spravato™), a nasal spray containing the S-enantiomer of ketamine. The launch was highly anticipated, as ketamine has been used off-label for several years and is in an area with unmet need.

ICER performed an extensive review of esketamine's role in treating TRD. They found the clinical evidence for esketamine plus background antidepressants demonstrated superiority compared to background antidepressants alone in patients with TRD; however, the evidence was insufficient to demonstrate a difference in health benefits compared to other strategies often employed in this population (e.g., electroconvulsive therapy [ECT], transcranial magnetic stimulation [TMS], antipsychotic augmentation, off-label IV ketamine). In addition, the majority of the reviewing panel felt uncertain of the long-term risks and benefits of esketamine, although esketamine was generally well-tolerated in short-term trials. While several patients may meet the criteria for TRD, the group also acknowledged that the role of esketamine is intended for patients with high severity and a high lifetime burden of illness.

Regarding long-term cost-effectiveness, ICER assessed nasal esketamine as having an incremental cost-effectiveness ratio exceeding \$175,000 per quality-adjusted life year (QALY) gained, considering it a low value for its announced list price and exceeding the budget impact threshold. ICER found that the fair value-based price benchmark for nasal esketamine (Spravato) should be \$17,700 to \$25,200 annually, requiring a discount of 25% to 52% from the list price. As a result, ICER issued an Affordability and Access Alert, noting that even at a recommended reduced price, only 20% to 30% of eligible patients with TRD could be treated before exceeding the budget impact threshold. ICER also recommended additional comparative, long-term, real-world effectiveness assessments, utilization management criteria for careful patient selection, and programs to ensure and encourage the proper management of patients using esketamine.

DRUG INFORMATION HIGHLIGHTS

- In conjunction with the ongoing public health emergency declaration related to the opioid crisis by the US Department of Health and Human Services (DHHS), the FDA announced that the Agency has invoked the Public Health Emergency prioritization factor to expedite the review of all abbreviated new drug applications (ANDAs) that reference new drug applications (NDAs) for drugs indicated for the emergency treatment of known or suspected opioid overdose. This would include ANDAs referencing nalmeferene (Baxter's Revex™; discontinued in 2008) and various forms of naloxone (Adapt's Narcan®; Kaleo's Evzio®).
- The intermittent shortage of epinephrine autoinjectors persists nationwide in the US. Backorders with periodic shipments to distributors continue for Impax's authorized generic (AG) versions of the discontinued Adrenaclick® and Mylan's EpiPen® 0.3 mg, EpiPen Jr® 0.15 mg, and their respective AGs. Availability continues for Kaleo's Auvi-Q® (3 strengths) and Teva's generic version of EpiPen (limited supply). Adamis' Symjepi®, has launched in both approved strengths (0.15 mg and 0.3 mg) to retail pharmacies nationwide. Teva's generic for EpiPen Jr has not yet launched in the US.
- Viiv reported that they will discontinue Rescriptor® (delavirdine) for business reasons. The anticipated final availability date of the antiretroviral (ARV) is January 2020.
- In conjunction with approved updated labeling, the FDA approved the reintroduction of Antivert® (meclizine) 25 mg chewable tablets to the US market.
- Altaire Pharmaceuticals issued a retail-level voluntary recall of select ophthalmic lubricating over-the-counter (OTC) drug products sold at CVS that are within expiry due to concerns with quality assurance. To date, Altaire has received no reports of adverse events. A full listing of impacted lots is available on the FDA recall page.
- Teva announced FDA approval of Airduo® Digihaler™, a breath-actuated, dry powder, digital inhaler of the combination fluticasone propionate, a corticosteroid, and salmeterol, a long-acting beta₂-adrenergic agonist. Airduo Digihaler has built-in sensors that connect to a companion mobile application and provides inhaler use information. Airduo Digihaler is indicated for the treatment of asthma in patients ≥ 12 years old. It is not for use in patients not adequately controlled on a long-term asthma control medication. The dosage is 1 oral inhalation twice daily. Approved strengths include (fluticasone propionate/salmeterol) 55/14 mcg, 113/14 mcg, and 232/14 mcg. Launch is anticipated in 2020.
- The FDA issued a warning to patients and healthcare professionals (HCPs) not to use products intended to be sterile that are produced by Pacifico National (doing business as AmEx Pharmacy, Melbourne, Florida) due to a lack of sterility assurance following a recent inspection. The FDA recommended that AmEx Pharmacy voluntarily recall all unexpired drugs intended to be sterile; however, to date, AmEx has not taken this action. The FDA is not aware of any reports of illness associated with use of these products.

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

- **August 2019:** ixekizumab (Taltz®); SC interleukin (IL)-17 inhibitor; axial spondyloarthritis; Eli Lilly.
- **August 2019:** pitolisant; oral histamine H3 receptor-antagonist/inverse agonist; narcolepsy; Harmony.
- **Aug-Sept 2019:** plasminogen; IV enzyme replacement; hypoplasminogenemia; Prometic Life Sciences.
- **August 14, 2019:** cefiderocol; IV cephalosporin; complicated urinary tract infection; Shionogi.
- **August 15, 2019:** loteprednol etabonate 0.25%; ophthalmic corticosteroid; dry eye disease; Kala.
- **August 16, 2019:** entrectinib; oral tyrosine kinase inhibitor; NSCLC (metastatic, ROS1+), solid tumors (NTRK fusion+); Genentech.
- **August 16, 2019:** tasimelteon (Hetlioz®); oral melatonin receptor agonist; jet lag disorder; Vanda.
- **August 19, 2019:** golodirsen; IV antisense oligonucleotide; Duchenne muscular dystrophy; Sarepta.
- **August 19, 2019:** lefamulin; IV/oral pleuromutilin antibiotic; community-acquired bacterial pneumonia; Nabriva.
- **August 20, 2019:** upadacitinib; oral Janus kinase (JAK) inhibitor; RA; Abbvie.
- **August 27, 2019:** istradefylline; oral adenosine A2a antagonist; Parkinson's disease "off" episodes; Kyowa Hakkō Kirin.
- **August 28, 2019:** oxycodone extended-release (ER); oral opioid agonist; chronic pain; Intellipharmaceuticals.
- **August 29, 2019:** NKTR-181; oral opioid agonist; chronic low back pain; Nektar.
- **September 2, 2019:** atezolizumab (Tecentriq®); IV programmed death-ligand 1 (PD-L1) inhibitor; non-squamous NSCLC (1st-line, EGFR/ALK- negative); Genentech.
- **September 3, 2019:** fedratinib; oral JAK inhibitor; myelofibrosis; Celgene.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs	
tiopronin delayed-release (Thiola® EC) Mission	<ul style="list-style-type: none"> • NDA approval 06/28/2019; Orphan Drug • Indicated in combination with high fluid intake, alkali, and diet modification to prevent cystine stones in adults and pediatrics weighing ≥ 20 kg with severe homozygous cystinuria who are not responsive to these measures alone • Reducing and complexing thiol • Tablets, delayed-release: 100 mg and 300 mg • Recommended starting dose in adults is 800 mg/day and in pediatrics weighing ≥ 20 kg is 15 mg/kg/day (avoid doses > 50 mg/kg/day); administer orally in 3 divided doses at the same time each day with or without food
immune globulin subcutaneous, human – klhw, 20% (Xembify®) Grifols	<ul style="list-style-type: none"> • BLA approval 07/03/2019 • Indicated for the treatment of primary humoral immunodeficiency in patients ≥ 2 years of age • Immune globulin (IG) • Injectable: 20% solution in 5 mL, 10 mL, 20 mL, and 50 mL single-use vials • Dosage is based on patients' serum immunoglobulin G (IgG) trough, pharmacokinetics, and clinical response; administer via SC infusion using up to 6 infusion sites simultaneously; administer 1 to 7 times per week; may self-administer with proper training; if switching from IVIG, administer first Xembify dose 1 week after the last IVIG dose – dose conversion is outlined in the prescribing information; if switching from SCIG, use the same weekly dose (grams) as previous SC product • Product availability is anticipated in late Q4, 2019
selinexor (Xpovio™) Karyopharm	<ul style="list-style-type: none"> • BLA approval 07/03/2019; Accelerated Approval; Orphan Drug; Priority Review • Indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received ≥ 4 prior therapies and whose disease is refractory to ≥ 2 proteasome inhibitors, ≥ 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody • Nuclear export inhibitor • Tablet: 20 mg • Recommended initial dose is 80 mg orally on days 1 and 3 each week
amlodipine (Katerzia™) Silvergate	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 07/08/2019 • Indicated for the treatment of hypertension in adult and pediatric patients ≥ 6 years of age and for coronary artery disease in adults • Calcium channel blocker • Suspension: 1 mg/mL in 150 mL • Recommended starting dose in adults is 5 mg orally once daily (may increase to 10 mg/day); pediatric starting dose is 2.5 mg once daily (may increase to 5 mg/day)
imipenem/cilastatin/relebactam (Recarbrio™) Merck	<ul style="list-style-type: none"> • NDA approval 07/16/2019; Priority Review; Qualified Infectious Disease Product • Indicated to treat complicated urinary tract infections (cUTI), including pyelonephritis, and complicated intra-abdominal infections (cIAI) caused by susceptible organisms in patients ≥ 18 years old who have limited or no alternative treatment options • Combination of a penem antibacterial, a renal dehydropeptidase inhibitor, and a beta-lactamase inhibitor • Injectable powder for reconstitution: 1.25 g SDV containing imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg • Recommended dosage is 1.25 g IV over 30 minutes every 6 hours; adjust dose for renal impairment • Product availability is expected in 2019

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; Q = Quarter; sBLA = Supplemental Biologics License Application; sNDA = Supplemental New Drug Application; 505(b)(2) = FDA approval pathway that allows for submission of data from studies not conducted by or for the applicant.

RECENT FDA APPROVALS *continued*

DRUG NAME MANUFACTURER	DESCRIPTION
Expanded Indications	
<p>pembrolizumab (Keytruda®) Merck</p>	<ul style="list-style-type: none"> • sBLA approval 06/10/2019; Priority Review <ul style="list-style-type: none"> » Expanded indication for use in combination with platinum and fluorouracil for first-line treatment of patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) » Expanded indication as a single agent for first-line treatment of patients with metastatic or unresectable recurrent HNSCC with tumors expressing PD-L1 (combined positive score ≥ 1) as determined by an FDA-approved test • sBLA approval 06/17/2019; Accelerated Approval; Orphan Drug; Priority Review <ul style="list-style-type: none"> » Expanded indication for metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and ≥ 1 other prior lines of therapy • Recommended dosage for HNSCC and SCLC is 200 mg IV over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression
<p>bictegravir/ emtricitabine/ tenofovir alafenamide (Biktarvy®) Gilead</p>	<ul style="list-style-type: none"> • sNDA approval 06/18/2019; Orphan Drug • Expanded indication as a complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection to include pediatric patients weighing ≥ 25 kg who have no ARV treatment history or to replace the current regimen in virologically suppressed patients on a stable ARV regimen who have no known resistance substitutions to any component of the product; it was previously approved only for adults • Recommended dosage is 1 tablet (50/200/25 mg) once daily; not recommended in patients with creatinine clearance < 30 mL/minute
<p>dexamethasone ocular insert (Dextenza®) Ocular Therapeutix</p>	<ul style="list-style-type: none"> • sNDA approval 06/20/2019 • Expanded indication to include treatment of ocular inflammation following ocular surgery; already indicated to treat ocular pain following ocular surgery • Recommended dosage is a single 0.4 mg insert placed into the lower lacrimal punctum/canalicus
<p>onabotulinumtoxinA (Botox®) Allergan</p>	<ul style="list-style-type: none"> • sBLA approval 06/20/2019; Priority Review • Expanded indication for the treatment of upper limb spasticity to include patients ages 2 to 17 years; previously indicated for treatment of upper limb spasticity in adults only • Recommended total dose in pediatrics is 3 to 6 units/kg (maximum 200 units) divided among the affected muscles; do not exceed 8 units/kg or 300 units in a 3-month interval
<p>ivacaftor/ tezacaftor + ivacaftor (Symdeko®) Vertex</p>	<ul style="list-style-type: none"> • sNDA approval 06/21/2019; Orphan Drug • Expanded indication to provide a new dosing regimen and use in patients weighing < 30 kg for the treatment of cystic fibrosis (CF) in patients 6 to < 12 years old who are homozygous for the <i>F508del</i> mutation or who have ≥ 1 mutation in the CF transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence • Recommended dosage: <ul style="list-style-type: none"> » For patients < 30 kg, 1 tablet of tezacaftor/ivacaftor 50/75 mg in the morning and 1 tablet of ivacaftor 75 mg in the evening » For patients ≥ 30 kg, 1 tablet of tezacaftor/ivacaftor 100/150 mg in the morning and 1 tablet of ivacaftor 150 mg in the evening » Administer doses orally approximately 12 hours apart; take with fat-containing food

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RECENT FDA APPROVALS *continued*

DRUG NAME MANUFACTURER	DESCRIPTION
Expanded Indications <i>continued</i>	
avatrombopag (Doptelet®) Dova	<ul style="list-style-type: none"> • sNDA approval 06/26/2019 • New indication for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment • Recommended initial dose is 20 mg orally once daily; adjust dose or frequency to maintain platelet count $\geq 50 \times 10^9/L$, not to exceed 40 mg/day
dupilumab (Dupixent®) Regeneron	<ul style="list-style-type: none"> • sBLA approval 06/26/2019; Priority Review • New indication as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis • Recommended dosage is 300 mg SC every other week
daratumumab (Darzalex®) Janssen	<ul style="list-style-type: none"> • sBLA approval 06/27/2019 • New indication for the treatment of multiple myeloma in combination with lenalidomide and low-dose dexamethasone for newly diagnosed adult patients ineligible for autologous stem cell transplant • Recommended dosage is 16 mg/kg actual body weight via IV infusion weekly during weeks 1 to 8, followed by every 2 weeks during weeks 9 to 24, followed by every 4 weeks from week 25 onwards until disease progression
eculizumab (Soliris®) Alexion	<ul style="list-style-type: none"> • sBLA approval 06/27/2019; Orphan Drug; Priority Review • New indication for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults who are anti-aquaporin-4 (AQP4) antibody positive • Recommended dosage for intraocular injection is 900 mg weekly for 4 weeks, followed by 1,200 mg for the fifth dose, administered 1 week later, followed by 1,200 mg every 2 weeks thereafter
apremilast (Otezla®) Celgene	<ul style="list-style-type: none"> • sNDA approval 07/19/2019; Orphan Drug • New indication for the treatment of adults with oral ulcers associated with Behçet's disease • Following a 6-day dose-escalation period, the maintenance dosage is 30 mg orally twice daily

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fda.gov icer-review.org