PERSPECTIVE ON THE RXPIPELINE

Understanding changes in the medication market and their impact.

EnvisionRx continuously monitors the drug pipeline. As treatment options change, we evaluate and share our perspective on the clinical benefits and impact in the market. Our Perspective on the Rx Pipeline reports provide ongoing insights from our team of clinical experts and considerations to protect and improve plan performance.

Included in this Edition

- Clinical Pipeline
- FDA Drug Approvals for March 2018
- New Indications
- Generic Approvals
- FDA Safety Update
- Drug Shortages and Discontinuations

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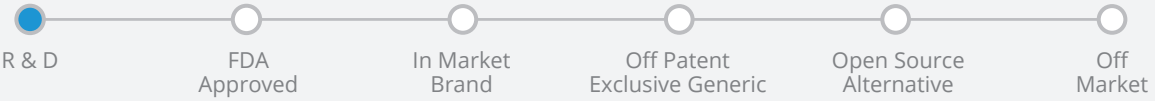
PIPELINE STAGE



avatrombopag

Manufacturer: Dova Pharmaceuticals
Indication/Use: Thrombopoietin (TPO) receptor agonist for the treatment of thrombocytopenia associated with liver disease (TLD) and idiopathic (immune) thrombocytopenic purpura (ITP)
Dosage Form: Orally once daily
Pipeline Stage: Pending NDA 05/21/2018

Thrombocytopenia is defined as having a platelet (PLT) count less than 150 x 10^9/L, which can be a serious issue for patients living with chronic liver disease, including complicating planned medical procedures due to the need for a PLT transfusion. In the U.S., there are 7.4 million patients with chronic liver disease and 70,000 have severe thrombocytopenia. In phase three clinical trials avatrombopage (AVA) was superior to placebo for increasing mean PLT counts on the day of procedure to 64 x 10^9/L. The most common treatment-emergent adverse effects (TEAE) were pyrexia, abdominal pain, nausea, and headache, which were similar between AVA and the placebo.[1]

AVA is an oral alternative to an intravenous platelet transfusion and will have a unique indication for treating thrombocytopenia in patients with chronic liver disease needing to undergo a procedure. AVA would be joining Promacta® (eltrombopag) as a second generation oral non-peptide TPO and Nplate® (romiplostim), a subcutaneous TPO.

Aimovig™ *erenumab*

Manufacturer: Amgen and Novartis
Indication/Use: Calcitonin gene-related peptide (CGRP) antagonist to prevent migraines
Dosage Form: 70mg or 140mg subcutaneous once monthly
Pipeline Stage: Pending BLA 05/17/2018

Up to 38 million Americans are effected by migraines. It is recommended that patients with frequent or severe headaches, who cannot take vasoconstrictors or who are refractory to acute treatment, should be treated with medication to prevent migraine attacks. Within the group of patients that currently use preventative medications, only 50-75% will have a 50% reduction in the frequency of headaches.[2] In clinical trials erenumab demonstrated a statistically significant 2.9-day reduction from baseline in monthly migraine days compared with a 1.8-day reduction in patients taking the placebo.[3] The safety profile of erenumab was found to be comparable to the placebo.

Erenumab is scheduled to be the first in a crowded pipeline of a novel therapeutic class, calcitonin gene-related peptide (CGRP) antagonists, to prevent migraines. CGRP antagonists are able to prevent migraines by blocking the actions of CGRP, stopping vasodilation and pain transmission. Erenumab is unique to its comparators in that erenumab's target is the CGRP receptor itself, not the peptide.[4] It offers an alternative solution for those members that have not been able to find successful outcomes with current options. Administration by the subcutaneous route is not preferred by patients and long term safety data is not yet available, however, this approval will represent a significant advancement in migraine therapy for the first time in decades.

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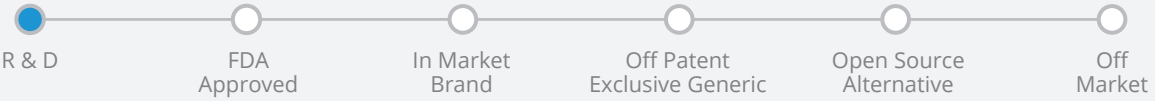

mogamulizumab

Manufacturer: Kyowa Hakko Kirin
Indication/Use: Cutaneous T-cell lymphoma (CTCL)
Dosage Form: Intravenous
Pipeline Stage: Pending BLA 06/04/2018

According to the National Cancer Database, an estimated 1,620 people were diagnosed with cutaneous T-cell lymphoma (CTCL) in 2016.[5] Systemic therapy is used as a primary treatment for patients with more severe stages of cancer, such as CTCL. Mogamulizumab targets the CC chemokine receptor 4 (CCR4), which is often expressed in cancers, including CTCL. The MAVORIC trial, a multicenter, international, open-label, randomized phase three trial, demonstrated significantly longer median progression-free survival with mogamulizumab (7.7 months) versus vorinostat (3.1 months). Overall response rates were noted in 28% of patients in the mogamulizumab group versus 4.8% in the control (vorinostat) group. Patients also reported quality of life outcomes were improved and the safety profile showed that common adverse events were manageable. [6]

Manufactured by Kyowa Hakko and approved in Japan since 2012, the monoclonal antibody's approval in the U.S. would offer another option to CTCL patients who have failed at least one previous systemic therapy. If approved mogamulizumab could compete with Istodax® (romidepsin), Adcetris® (brentuximab vedotin), and Targretin® (bexarotene).

Glossary of Terms
BLA - Biologics License Application
NDA - New Drug Application

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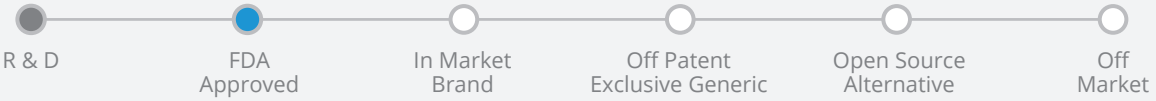
Drug Approvals

PIPELINE STAGE



Ilumya™ *tildrakizumab-asmn*

Manufacturer: Sun Pharmaceutical Industries, Inc.
Indication/Use: Plaque Psoriasis
Dosage Form: Subcutaneous
Traditional or Specialty: Specialty

On March 20, 2018, the FDA approved Ilumya (tildrakizumab-asmn) to treat moderate-to-severe plaque psoriasis. Ilumya is a humanized, anti-IL 23p19 monoclonal antibody administered subcutaneously every 12 weeks after the completion of the initial starting doses. Clinical trials resulted in significant clinical improvement with Ilumya compared to the placebo when evaluating 75% of skin clearance.

For more information: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=761067

Trogarzo™ *ibalizumab-uiyk*

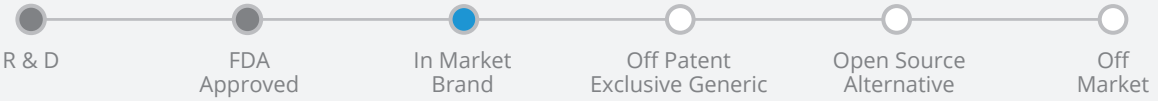
Manufacturer: TaiMed Biologics USA Corp
Indication/Use: Multi-drug resistant human immunodeficiency virus (HIV)
Dosage Form: Intravenous
Traditional or Specialty: Specialty

Trogarzo (ibalizumab-uiyk) is a CD4-directed post attachment HIV inhibitor approved by the FDA on March 6, 2018 for those treatment-experienced adults whose HIV infections cannot be successfully treated with other available therapies. Trogarzo is administered by IV infusion once every 14 days and used in combination with other antiretroviral medications.

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

New Indications

PIPELINE STAGE



Blincyto® *blinatumomab*

Manufacturer: Amgen
Indication/Use: Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) and minimal residual disease (MRD)-positive B-cell precursor ALL
Dosage Form: Injection
Traditional or Specialty: Specialty
Date of Original Approval: December 2014

Blincyto is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). On March 29, 2018, the FDA approved the expanded indication to patients with minimal residual disease (MRD)-positive B-cell precursor ALL.

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

Tasigna® *nilotinib*

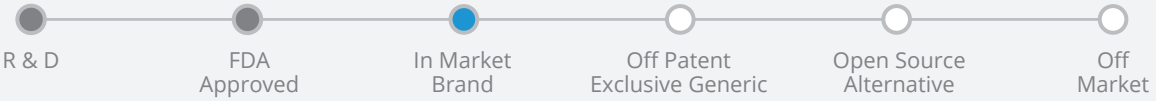
Manufacturer: Novartis
Indication/Use: Philadelphia chromosome positive chronic myelogenous leukemia (CML)
Dosage Form: Capsules
Traditional or Specialty: Specialty
Date of Original Approval: October 2017

Tasigna is a BCR-ABL tyrosine kinase inhibitor originally approved for treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML). On March 22, 2018, Novartis announced that the FDA expanded this indication to include pediatric patients one year of age and older as a first-line or second-line option for those in chronic phase CML. This follows closely after a new dosing regimen approval in December 2017 in which the FDA approved label changes recommending a discontinuation in eligible patients that have a sustained molecular response for at least three years.

For more information: http://www.tasigna.com/

New Indications

PIPELINE STAGE



Adcetris® *brentuximab vedotin*

Manufacturer: Seattle Genetics
Indication/Use: Relapsed and refractory Hodgkin lymphoma and stage III or IV classical Hodgkin lymphoma
Dosage Form: Injection
Traditional or Specialty: Specialty
Date of Original Approval: August 2011

Adcetris is a drug designed as a combination of antibody and drug that targets the CD30 site on lymphoma cells. Originally approved for relapsed and refractory Hodgkin lymphoma in 2011, clinical trials since that time have demonstrated the benefits of Adcetris as a first-line treatment of stage III or IV classical Hodgkin lymphoma in combination with chemotherapy. Based on significant improvement in clinical trials, on March 20, 2018, the FDA approved the expanded use to this patient population.

For more information: https://adcetrisavd.com

Hizentra® *immune globulin subcutaneous (human)*

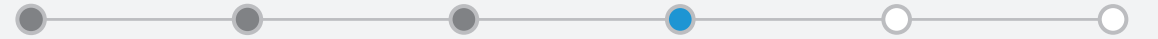
Manufacturer: CSL Behring
Indication/Use: Primary humoral immunodeficiency and chronic inflammatory demyelinating polyneuropathy (CIDP)
Dosage Form: Subcutaneous
Traditional or Specialty: Specialty
Date of Original Approval: March 2010

Hizentra is a subcutaneously administered 20% concentrated human immunoglobulin originally approved to treat primary humoral immunodeficiency. On March 16, 2018, it was approved by the FDA to be used as a maintenance therapy for patients with chronic inflammatory demyelinating polyneuropathy (CIDP). Immunoglobulin therapy in CDIP patients has been shown to prevent relapses of neuromuscular impairments and disability. Hizentra is the first and currently only subcutaneous immunoglobulin to carry this indication in adults.

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

Generic Approvals

PIPELINE STAGE



Brand Name	Generic Name	Manufacturer of Entrants	Indication	Approved	Anticipated Launch Date
Adcirca®	Tadalafil	TBD	Pulmonary Arterial Hypertension	Pending	May 2018
Aloxi® 0.25mg/5ml ONLY	Palonosetron	Accord, Cipla, Dr. Reddy's, Sandoz, Teva	Chemotherapy induced nausea or vomiting	Yes	
Coreg CR*	Carvedilol Phosphate	TBD	Ischemic Heart Disease; HTN; HF	Pending	May 2018
Emsam®	Selegiline	TBD	Depression	Pending	June 2018
Invega Trinza®	Paliperidone Palmitate	TBD	Schizophrenia; Schizoaffective disorder	Pending	May 2018
Lexiva (oral suspension)	Fosamprenavir Calcium	TBD	HIV or AIDS	Pending	June 2018
Norvir® 100mg Tab ONLY	Ritonavir	West-Ward, Zydus	HIV	Yes	
Onexton®	Benzoyl Peroxide; Clindamycin Phosphate	TBD	Acne Vulgaris	Pending	June 2018
Reyataz® (150mg, 200mg, 300mg)*	Atazanavir Sulfate	TBD	HIV or AIDS	Pending	June 2018
Safyral®	Drospirenone; Ethinyl Estradiol; Levomefolate Calcium	Sandoz, Lupin	Pregnancy prevention	Yes	
Viagra®*	Sildenafil Citrate	TBD	Erectile dysfunction	Pending	June 2018

*Loss of 180-day exclusivity.

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FDA Safety Updates

Drug Safety Communication

Essure® - On April 9, 2018, the FDA restricted sales of the Essure device to only doctors and healthcare facilities who use the FDA-approved *Patient-Doctor Discussion Checklist — Acceptance of Risk and Informed Decision Acknowledgement*. In January, the FDA conducted a search of the Manufacturer and User Facility Device Experience (MAUDE) database and found 26,773 reports related to Essure. The FDA wants to ensure that each and every woman who receives Essure has been informed of the risks and benefits before getting the device implanted.

For more information: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452254.htm

Drug Shortages and Discontinuations

Carbidopa and Levodopa Extended-Release Tablets
Accord has carbidopa and levodopa 50mg/200mg extended-release tablets on back order and the company cannot estimate a release date. Sun Pharma has carbidopa and levodopa 25mg/100mg and 50mg/200mg extended-release tablets available in limited supply.

Diclofenac 0.1% Ophthalmic Solution
Akorn has diclofenac 0.1% ophthalmic solution on long-term back order. Sandoz has diclofenac 0.1% ophthalmic solution in 2.5mL and 5mL bottles on back order and was predicting an estimated release date in early- to mid-April 2018.

Dorzolamide 2% and Timolol 0.5% Ophthalmic Solution
Akorn has dorzolamide 2% and timolol 0.5% ophthalmic solution in 10mL bottles on allocation. The company has Cosopt® 2%/0.5% ophthalmic solution in 10mL bottles on back order and cannot estimate a release date. Sandoz has dorzolamide 2% and timolol 0.5% ophthalmic solution in 10mL bottles on back order and the company was predicting an estimated release date of mid- to late-April 2018. Teva has dorzolamide 2% and timolol 0.5% ophthalmic solution in 10mL bottles on back order and was predicting an estimated release date of late-April 2018.

Furosemide Tablets
Mylan has furosemide 40mg tablets in 100 count on intermittent back order and estimates a release date of early-May 2018. Teva has furosemide 20mg and 40mg tablets in 100 and 1,000 count bottles temporarily unavailable and cannot estimate a release date. West-Ward has furosemide 20mg tablets in 100 count and 1,000 count bottles on allocation. The 40mg tablets in 100 count and 1,000 count bottles are also on allocation.

Quilichews chewable tablet and suspension
Pfizer has Quillivant XR® 5mg/mL extended-release oral suspension in 60mL bottles on back order and estimates a release date of late-May 2018. The QulliChews® 20mg, 30mg and 40mg tablets are on back order and the company was predicting an estimated release date of mid-April 2018.

For more information on drug shortages: https://www.ashp.org/drug-shortages/current-shortages

Our Clinical Steering Committee

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

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

Kel Riley, MD
Chief Medical Officer

Learn more ways to improve patient and plan outcomes

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Sources

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[4] Amgen. Amgen Reports Aimovig (Erenumab) Met All Primary and Secondary Endpoints in Unique Phase 3b Studying Episodic Migraine Patient Who have Failed Multiple Prior Preventative Treatments. Media-Rel 2018

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EnvisionRx is a Pharmacy Benefit Manager (PBM), providing affordable and effective prescription drug coverage for employers and health plans. Using its proprietary EnvisionCare model, EnvisionRx optimizes all aspects of the pharmacy care experience to consistently achieve better patient and plan outcomes.

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