RXPIPELINEQ1UPDATE

Learn what medications are in development and how their expected approval will impact care.

EnvisionRx continuously monitors the drug pipeline, keeping an eye on new drugs in development that will profoundly impact care. Our Rx Pipeline Update provides information on those medications that are nearing approval, sharing differentiators and impactful drug details to help you prepare for the future.

Included in this Edition

Drug Name	Manufacturer	Indication/Use	Expected FDA Decision Date
andexanet alfa	Portola Pharmaceuticals	Antidote for oral anticoagulants	02/02/2018
bictegravir/emtricitabine/ tenofovir alafenamide	Gilead	HIV	02/12/2018*
ibalizumab	Thera Technologies	HIV	04/03/2018
tezacaftor/ivacaftor	Vertex	Cystic fibrosis	02/28/2018
tildrakizumab	Sun Merck and Co Samsung	Plaque psoriasis	03/2018

* Approved during publishing

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andexanet alfa

Class: anticoagulant antidote

Manufacturer: Portola Pharmaceuticals

Administration: Intravenous

Andexanet alfa Provides Alternative for Major Bleeding Incidents

PIPELINE STAGE

Early Clinical Trials | Phase III Clinical Trials | **Estimated FDA Review Date (PDUFA)** | FDA Approval | Drug Launch to Market

INDICATION

Reversal of anticoagulant activity of Factor Xa inhibitors

ADMINISTRATION

IV infusion

POSITIVES

- First and only reversal agent for Xa inhibitors, hemostasis in 79% of patients

NEGATIVES

- 18% of patients experience a thrombotic event

CLINICAL EFFECTIVENESS

Compared to available options, is this drug better for treatment?

UNPROVEN | EQUIVALENT | **BETTER**

PAYER IMPACT

How will this influence Rx spend?

DECREASE PER Rx | **NO CHANGE** | INCREASE PER Rx

FDA ACTIONS

- December 2015 BLA submitted
- February 2016 Biologics License Application (BLA) accepted by FDA
- August 2016 CRL issued for manufacturing concerns

Therapeutic Indications

Andexanet alfa, also known as Andexxa,™ is in development as a novel antidote to the anticoagulant effects of factor Xa inhibitors, such as Xarelto® and Eliquis.® Once andexanet alfa binds to the factor Xa inhibitor, the factor Xa inhibitor is no longer able to inhibit the coagulation process and allows for the restoring of normal hemostasis.

Clinical Briefing

The recombinant modified human factor Xa decoy protein, andexanet alfa, was studied in a multicenter, prospective, open-label, single-group designed trial for patients with acute major bleeding. Patients were eligible if they had been receiving apixaban, rivaroxaban, edoxaban or enoxaparin within 18 hours of the acute major bleed. The dosing of andexanet alfa was dependent on the factor Xa inhibitor being taken due to the plasma protein binding and distribution of the different products. Dosages ranged from 400mg IV bolus and 480mg IV infusion, to 800mg IV bolus and 960mg IV infusion. Based on the interim data analysis published in the *New England Journal of Medicine,* 79% of patients evaluated for efficacy achieved excellent or good hemostasis (stoppage of bleeding). There were no reports of infusion reactions or neutralizing antibody development. Thrombotic events (clotting) occurred in 18% of patients, lasting anywhere from three days up to 30 days post treatment. Based on these interim results, the expectation is the trend will stay the same after full enrollment, when the study can provide statistical power.

Place in Therapy

For the treatment and prevention of venous thromboembolism (clots), factor Xa inhibitors have demonstrated that they can be both safe and effective. The risk of these agents is the association with major and even fatal bleeding events, which are currently difficult to treat with no reversal agent. Approximately 1-3% of patients taking an oral factor Xa inhibitor experience a major bleed and another 1% require emergency surgery based on the phase 3 clinical trial results. Andexanet alfa has demonstrated clinical efficacy to stop bleeding in this patient population with a thrombotic event rate of 18% in the interim analysis.

bictegravir/emtricitabine/tenofovir alafenamide

Class: Integrase strand transfer inhibitor (INSTI), and a dual nucleoside/nucleotide reverse transcriptase inhibitors (NRTI)

Manufacturer: Gilead

Administration: Oral

New HIV Treatment that Limits Nausea and Treats Those Co-Infected with Hepatitis B

PIPELINE STAGE

Early Clinical Trials | Phase III Clinical Trials | Estimated FDA Review Date (PDUFA) | **FDA Approval** | Drug Launch to Market

INDICATION

Treatment for HIV1 infection

ADMINISTRATION

Oral

POSITIVES

- Oral once daily regimen
- Less nausea

NEGATIVES

- Many competitors

CLINICAL EFFECTIVENESS

Compared to available options, is this drug better for treatment?

PAYER IMPACT

How will this influence Rx spend?

FDA ACTIONS

- June 2017 NDA submitted
- August 2017 granted FDA Priority Review designation
- February 2018 FDA approval

Therapeutic Indications

Bictegravir, a novel, potent integrase strand transfer inhibitor, is combined with emtriciabine, a nucleoside reverse transcriptase inhibitor, and tenofovir alafenamide, a nucleotide analog reverse transcriptase inhibitor.

Clinical Briefing

In a randomized, double-blind, multi-center, active-controlled, non-inferiority trial published in the ***Lancet,*** patients were given a fixed dose of either bictegravir/emtricitabine/tenofovir alafenamide (B/E/TA) or coformulated doluegravie/abacavir/lamivudine once daily for 144 weeks. At week 48, HIV1 RNA <50 copies/mL was achieved in 92.4% of B/E/TA patients versus the comparator group (93.0%). The number and type of adverse events was similar between the groups, with the exception of nausea, which occurred less frequently in B/E/TA patients. There are three other clinical trials that demonstrate the non-inferiority of B/E/TA to various HIV combination therapies and regimens that contain boosting agents. These trials show the same trend in adverse events.

Place in Therapy

B/E/TA will be entering a competitive market with Genvoya,® Odefsey,® and Triumeq.® A differentiator for this product will be the lower incidence of nausea. Additionally, it is a guideline-recommended treatment for individuals co-infected with HIV and Hepatitis B that does not require HLA-B*5701 testing. This drug was granted FDA approval at the time of publishing and will be marketed as Biktarvy.

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ibalizumab

Class: Entry inhibitor

Manufacturer: TaiMed Biologics; Theratechnologies

Administration: Intravenous

Breakthrough Therapy On Horizon for Multi-Drug Resistant HIV Patients

PIPELINE STAGE

Early Clinical Trials | Phase III Clinical Trials | **Estimated FDA Review Date (PDUFA)** | FDA Approval | Drug Launch to Market

INDICATION

Treatment of adults with HIV-1 infection resistant to one or more agents in three different classes

ADMINISTRATION

2,000mg IV infusion loading dose then 800mg IV every two weeks

POSITIVES

- Novel mechanism of action
- Infrequent dosing

NEGATIVES

- IV administration
- Not for initial therapy

CLINICAL EFFECTIVENESS

Compared to available options, is this drug better for treatment?

PAYER IMPACT

How will this influence Rx spend?

FDA ACTIONS

- 2014 Orphan drug designation
- 2015 Break through therapy designation
- 2017 Granted priority review

Therapeutic Indications

ibalizumab is an investigational humanized monoclonal antibody designed to bind to the second extracellular domain of the CD4+ T cell receptor, which blocks HIV from attaching to the cell and infecting it. This is a new mechanism of action to treat multi-drug resistant HIV-1, the first in this therapeutic class in almost ten years.

Clinical Briefing

In a 24-week phase three registration study of 40 patients with multi-drug resistant HIV-1 infection, ibalizumab was able to decrease the viral load compared to their current therapy alone by > 0.5 log 10 in 83% of patients versus 3% of control patients. After patients received optimized background regimens (OBR) on the 14th day of the clinical trial, 43% of patients had an undetectable viral load and 50% of patients had <200 copies.

While there were four reported deaths during the clinical trial—one death each due to liver failure, Kaposi sarcoma, end-stage AIDS, and lymphoma—none were believed to be attributed to the study drug. Treatment emergent adverse events included dizziness (10%), fatigue (5%), nausea/vomiting (5%) and rash (2.5%). One participant of the 17 that received ibalizumab with OBR had immune reconstitution inflammatory syndrome (IRIS), which caused the discontinuation of the study drug.

Place in Therapy

It is estimated that with the 1.2 million patients in the U.S. living with HIV, about 10,000 patients have multi-drug resistant conditions. Ibalizumab offers a beneficial therapy where there currently is not a standard approach to care. This will be used as an add-on therapy and not substitutable for current therapies or intended for first-line therapy options. This novel mechanism of action needs to be administered by IV infusion, but with infrequent dosing of every two weeks after the initial loading dose. While there were not any strong safety signals in clinical trials, there was a report of immune reconstitution inflammatory syndrome (IRIS), which can be potentially life threatening.

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tezacaftor/ivacaftor

Class: Cystic fibrosis transmembrane conductance regulator (CFTR)

Manufacturer: Vertex Pharmaceuticals

Administration: Oral

A New Alternative for the Treatment of Cystic Fibrosis

PIPELINE STAGE

Early Clinical Trials | Phase III Clinical Trials | **Estimated FDA Review Date (PDUFA)** | FDA Approval | Drug Launch to Market

INDICATION

Treatment of cystic fibrosis (CF) with specific mutations

ADMINISTRATION

Oral

POSITIVES

- Oral medication
- Another treatment option

NEGATIVES

- Separate dose of ivacaftor needed in evening for heterozygous patients

CLINICAL EFFECTIVENESS

Compared to available options, is this drug better for treatment?

PAYER IMPACT

How will this influence Rx spend?

FDA ACTIONS

- Priority review
- Orphan drug designation
- Breakthrough status

Therapeutic Indications

Cystic fibrosis is caused by a defective or missing transmembrane regulator gene, which results in poor flow of salt and water into or out of cells in organs, including the lungs. Tezacaftor is in development to increase the amount of protein and help the flow of salt and water into and out of cells. Ivacaftor is approved and marketed as Kalydeco,® which is a CFTR corrector.

Clinical Briefing

The EVOLVE clinical trial of 510 patients used a randomized, double-blind, multicenter, placebo-controlled, parallel-group, design to evaluate the combination of tezacaftor/ivacaftor therapy in patients 12 years of age and older who had cystic fibrosis and were heterozygous or homozygous for the specific mutation Phe508del. In patients with the homozygous Phe508del mutation, the combination product showed improvement in percent predicted forced expiratory volume in one second (FEV1) versus the placebo (difference of 4%). Additionally, the number of pulmonary exacerbations through week 24 decreased for the study drug versus the placebo (78 events vs. 122 events). The benefit was not as robust in patients with heterozygous Phe508del mutations. In this cohort, the benefit of tezacaftor/ivacaftor versus ivacaftor alone was smaller (6.8% vs. 4.7%). The most common adverse events (>10%) were infective pulmonary exacerbation of CF, cough and coughing blood.

Place in Therapy

Cystic fibrosis is a rare genetic disorder that can be life-threatening and affects around 30,000 people, with approximately 1,000 new cases diagnosed each year.

Tezacaftor is joining Orkambi,® a combination of lumacaftor and ivacaftor, in the CF area. A differentiator for tezacaftor is a reduced risk of bronchoconstriction. Respiratory events were reported in 20-30% of patients in clinical trials with Orkambi.®

The Institute for Clinical and Economic Review (ICER) is expected to have a final report of the review of therapies for cystic fibrosis, including tezacaftor/ivacaftor by May of 2018.

tildrakizumab

Class: Anti-interleukin monoclonal antibody

Manufacturer: Sun Pharmaceutical Industries, Inc.

Administration: Subcutaneous

Tildrakizumab Adds Another Plaque Psoriasis Medication to the Crowded Class

PIPELINE STAGE

Early Clinical Trials | Phase III Clinical Trials | **Estimated FDA Review Date (PDUFA)** | FDA Approval | Drug Launch to Market

INDICATION

Treatment of moderate to severe plaque psoriasis

ADMINISTRATION

100mg/200mg SC week 0 and 4, then every 12 weeks

POSITIVES

- Subcutaneous self-injectable with infrequent dosing after initial loading
- Sound safety profile

NEGATIVES

- Competitive market

CLINICAL EFFECTIVENESS

Compared to available options, is this drug better for treatment?

UNPROVEN | EQUIVALENT | BETTER

PAYER IMPACT

How will this influence Rx spend?

DECREASE PER Rx | NO CHANGE | INCREASE PER Rx

FDA ACTIONS

- May 2017 FDA accepts BLA

Therapeutic Indications

Tildrakizumab joins many drugs in a rapidly expanding class of therapeutic options to treat moderate to severe plaque psoriasis. The IL-23p19 monoclonal antibody is designed to block the cytokine IL-23, which controls the pathogenic cells responsible for the inflammatory process of psoriasis.

Clinical Briefing

In a robust clinical trial portfolio, tildrakizumab was studied in two three-part, parallel group, double-blind, randomized controlled studies in the reSURFACE series. In the first reSURFACE trial, tildrakizumab was vetted against a placebo and in the second trial, tildrakizumab was studied against etanercept (Enbrel) as an active comparator. During the first trial, at week 12, 192 patients (62%) in the 200mg group and 197 patients (64%) in the 100mg group achieved PASI 75, compared with nine patients (6%) in the placebo group ($p<0{\cdot}0001$). In the second trial, at week 12, 206 patients (66%) in the 200mg group and 188 patients (61%) in the 100mg group achieved PASI 75, compared with nine patients (6%) in the placebo group and 151 patients (48%) in the etanercept group ($p<0{\cdot}0001$). Serious adverse events were similar and low in all groups in both trials.

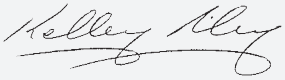
Place in Therapy

Psoriasis is a chronic, immune-mediated disease that manifests most commonly on the skin and effects an estimated 7.5 million people in the U.S. Tildrakizumab joins a crowded therapeutic class with Cosentyx® (secukinumab), Stelara® (usteknumab), Taltz® (ixekizumab) and Siliq™ (brodalumab).

Our Clinical Steering Committee

The Envision Clinical Steering Committee brings together leaders 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.



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