OPTUMRx®

RxOutlook®

4th Quarter 2017

Pending drug approvals

Drug Name	Manufacturer	Indication/Use	Expected FDA Decision Date
abiraterone acetate (Yonsa™)	Churchill/Iroko	Prostate cancer	3/19/2018
bictegravir/emtricitabine/ tenofovir alafenamide	Gilead	HIV-1	2/12/2018
emicizumab	Roche/Chugai/JW Pharmaceuticals	Hemophilia A	2/23/2018
ibalizumab	Theratechnologies	Human immunodeficiency virus type 1 (HIV-1)	1/3/2018
ivacaftor/tezacaftor	Vertex/Royalty Pharma	Cystic fibrosis	2/28/2018
netarsudil (Rhopressa™)	Aerie	Glaucoma and ocular hypertension	2/28/2018
pegvaliase (Peg-Pal)	BioMarin/Merck	Phenylketonuria	5/28/2018

abiraterone acetate (Yonsa)

Manufacturers: Churchill/Iroko

Therapeutic use

Churchill's abiraterone acetate, also known as Yonsa, is in development for use in combination with methylprednisolone for the treatment of patients with metastatic castration-resistant prostate cancer.

- In combination with methylprednisolone for the treatment of metastatic castration-resistant prostate cancer

Clinical profile

Abiraterone acetate is an androgen biosynthesis inhibitor. It is also currently available as Zytiga® by Janssen Biotech and indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

Because of an existing patent by Janssen Biotech, which prohibits the use of abiraterone acetate in combination with prednisone for prostate cancer, Churchill is pursuing Yonsa for use in combination with methylprednisolone. Moreover, Yonsa is being developed as an ultramicrosized formulation to enhance the bioavailability relative to Zytiga.

Yonsa was evaluated in bioequivalence studies and demonstrated a comparable pharmacokinetic profile to Zytiga.

In a food effect study, administration of food raised the concentrations of Yonsa and Zytiga compared to the fasted state; however, Yonsa's maximum concentrations were significantly lower compared to Zytiga's (6.5x higher vs. 17x higher). Churchill is touting that this difference reduces the risk of adverse effects with Yonsa vs. Zytiga; however, this has not been clinically demonstrated. Moreover, the FDA drug label for Zytiga states that abiraterone acetate should be given on an empty stomach and no food consumed for at least 2 hours before the dose and at least 1 hour after the dose. Yonsa is expected to carry the same directions, thus, if patients follow the dosing directions these differences in concentration are unlikely to be clinically meaningful.

- Androgen biosynthesis inhibitor
- Oral formulation
- Bioequivalent to Zytiga
- Warnings: similar to Zytiga
- Dose: 500 mg once daily

Because Yonsa and Zytiga share the same active ingredient, Yonsa is expected to carry the same safety concerns as Zytiga. Zytiga includes warnings and precautions for hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess; adrenocortical insufficiency; and hepatotoxicity.

The anticipated dosage for Yonsa is 500 mg orally once daily. In contrast, Zytiga is dosed 1,000 mg orally once daily.

Continued…

abiraterone acetate (Yonsa) (continued...)

Competitive environment

Yonsa is an oral agent touted as increasing the bioavailability of abiraterone acetate compared to Zytiga, thus allowing lower doses of Yonsa to be administered.

While the reduced dose may lower the risk for adverse events, this has not been clinically demonstrated. Yonsa is not a unique product and a comparable product, Zytiga, is already commercially available.

The monthly WAC for Zytiga is $9,396.

- Advantages: oral, improved bioavailability vs. Zytiga
- Disadvantages: not unique, related product is available (ie, Zytiga)
- Monthly WAC for Zytiga = $9,396

Expected FDA decision date

An FDA decision regarding the approval of Yonsa is expected by March 19, 2018.

- PDUFA: 3/19/2018

bictegravir/emtricitabine/tenofovir alafenamide

Manufacturer: Gilead

Therapeutic use

Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a fixed-dose combination product for the treatment of HIV.

- Treatment of HIV

Clinical profile

B/F/TAF consists of an integrase strand transfer inhibitor (bictegravir), a nucleoside reverse transcriptase inhibitor (emtricitabine), and a nucleotide analog reverse transcriptase inhibitor (tenofovir alafenamide).

There are four pivotal trials for B/F/TAF. In all four trials, B/F/TAF was non-inferior to various HIV combination regimens, including Triumeq® (abacavir/dolutegravir/lamivudine) and regimens containing boosting agents, such as ritonavir or cobicistat.

The most common adverse events were headache and diarrhea.

In the clinical trials, B/F/TAF was administered orally once daily.

- Integrase strand transfer inhibitor and reverse transcriptase inhibitors
- Oral formulation
- Non-inferior to HIV combination alternatives
- Common adverse events: headache, diarrhea
- Dose: once daily

Competitive environment

The primary benefit of B/F/TAF is its convenience. B/F/TAF reduces the total number of pills that patients require because the three components are formulated into a fixed-dose formulation. In addition, B/F/TAF is touted as causing less nausea than comparator regimens.

However, if approved, B/F/TAF will be entering a highly competitive market (eg, Genvoya®, Odefsey®, Triumeq).

For reference, the wholesale acquisition cost (WAC) for Triumeq is approximately $2,600 per month.

- Advantages: patient convenience, may cause less nausea than comparators
- Disadvantage: highly competitive market
- Monthly WAC for Triumeq = $2,600

Expected FDA decision date

B/F/TAF was granted an orphan drug designation for the treatment of pediatric HIV.

An FDA decision regarding the approval of B/F/TAF is expected by February 12, 2018.

- Orphan drug
- PDUFA: 2/12/2018

emicizumab

Manufacturers: Roche/Chugai/JW Pharmaceuticals

Therapeutic use

Emicizumab is in development for prophylactic treatment of adults, adolescents, and children with hemophilia A with factor VIII inhibitors.

Hemophilia is a rare genetic disorder affecting an estimated 20,000 Americans.

Hemophilia A, also known as classic hemophilia, is caused by a defective or missing factor VIII protein, which is necessary for proper blood clot formation.

- Prophylaxis of patients with hemophilia A with factor VIII inhibitors

Clinical profile

Emicizumab is a bi-specific antibody that simultaneously targets factor IXa and factor X. Emicizumab acts as a factor VIII mimetic, which permits blood coagulation regardless of the presence of factor VIII inhibitors.

In a pivotal trial, emicizumab-treated patients achieved significantly less bleeding events and an 87% reduction in annualized bleeding rate vs. the non-prophylactic group (i.e. those not given emicizumab; $p < 0.001$).

The most common adverse events reported in trials were injection site reactions, headache, upper respiratory tract infections, nasopharyngitis, and arthralgia.

In clinical trials, the dosing for emicizumab was weight-based and administered subcutaneously (SC) once weekly.

- Factor IXa/Factor X bispecific antibody
- SC formulation
- 87% reduction in annualized bleeding rate
- Common adverse events: injection site reactions, headache, upper respiratory tract infections, nasopharyngitis, and arthralgia
- Dose: weight-based once weekly

Competitive environment

Emicizumab works by a novel MOA and is a useful treatment for patients who have developed inhibitors to factor VIII. Unlike many antihemophilic treatments, which are administered IV, emicizumab is given SC. Moreover, it is only dosed once weekly and no neutralizing antibodies were observed in its pivotal trial.

However, thrombotic events have been reported in some patients receiving prothrombin. In addition, there are no head-to-head trials comparing emicizumab to alternative approaches.

The estimated average annual healthcare cost associated with hemophilia A in patients with inhibitors is $696,279.

- Advantages: novel MOA, useful in patients with factor VIII inhibitors, SC administration, once weekly dosing, no neutralizing antibodies
- Disadvantages: thrombotic events were reported, no head-to-head trials
- Average annual healthcare costs for hemophilia A in patients with inhibitors = $696,279 per patient

Expected FDA decision date

Emicizumab was granted breakthrough and orphan drug designations.

An FDA decision regarding the approval of emicizumab is expected by February 23, 2018.

- Orphan drug
- Breakthrough status
- PDUFA: 2/23/2018

ibalizumab

Manufacturer: Theratechnologies

Therapeutic use

Ibalizumab is in development for the treatment of adult patients with human immunodeficiency virus type 1 (HIV-1) infection that is resistant to at least 1 agent in three different drug classes used to treat HIV-1 infection.

This form of HIV is referred to as multi-drug resistant or 3-class resistant HIV.

- Treatment of adults with HIV-1 infection resistant to ≥ 1 agent in three different drug classes

Clinical profile

Ibalizumab is a CD4 monoclonal antibody. It inhibits the entry of the HIV-1 virus into CD4-positive T-cells, thereby, blocking the spread of the virus. It is considered a non-immunosuppressive monoclonal antibody.

In a phase 3 single-arm trial, 83% of patients achieved ≥ 0.5 $\log_{10}$ reduction in viral load ($p < 0.0001$) and 60% of patients achieved ≥ 1.0 $\log_{10}$ reduction in viral load from baseline ($p < 0.0001$). Patients were optimized to a background drug regimen for HIV.

While there were four fatalities in the trial, these cases were not believed to be treatment related. At the time of death, the patients had Kaposi sarcoma, end-stage acquired immunodeficiency syndrome (AIDS), lymphoma, or liver failure.

The most notable safety concern was immune reconstitution inflammatory syndrome (IRIS), which occurred in 1 patient in the trial. IRIS is an exaggerated inflammatory reaction that occurs in response to the presence of a microorganism. It is believed to result from the recovery of the immune system following certain treatments such as an antiretroviral regimen. IRIS is potentially life-threatening.

In the trial, ibalizumab was given as an initial loading dose of 2,000 mg intravenously (IV), followed by 800 mg IV every 2 weeks.

- CD4 attachment inhibitor
- IV formulation
- 83% of patients achieved ≥ 0.5 $\log_{10}$ in viral load
- Serious adverse event: IRIS
- Dose: 2,000 mg loading dose, followed by 800 mg every 2 weeks

Competitive environment

Ibalizumab offers a significant benefit to patients with multi-drug resistant HIV. Currently, there is no standard treatment available for these patients. Moreover, ibalizumab employs a novel mechanism of action (MOA), requires dosing once every 2 weeks, and no antibodies were detected in its major clinical trial.

Nonetheless, ibalizumab requires IV administration and is not intended as first line therapy for HIV. There is also the potential for IRIS, a serious and potentially life-threatening adverse event.

In a 1 million member health plan, an estimated 100 patients are believed to have multi-drug resistant HIV.

- Advantages: benefit in multi-drug resistant HIV, novel MOA, infrequent dosing, no antibodies detected in trial
- Disadvantages: requires IV administration, not for initial therapy, risk of IRIS

Expected FDA decision date

Ibalizumab was granted fast track, breakthrough, and orphan drug designations.

An FDA decision regarding the approval of ibalizumab is expected by January 3, 2018.

- Orphan drug
- Fast track status
- Breakthrough status
- PDUFA: 1/3/2018

ivacaftor/tezacaftor

Manufacturers: Vertex/Royalty Pharma

Therapeutic use

Ivacaftor/tezacaftor (IVA/TEZ) is a combination product in development for the treatment of cystic fibrosis (CF) patients ≥ 12 years of age who have two copies of the F508del mutation or one F508del mutation and one residual mutation that is responsive to IVA/TEZ.

- Treatment of CF patients ≥ 12 years of age who have at least one copy of the F508del mutation

Clinical profile

IVA/TEZ is a combination product containing a CF transmembrane conductance regulator (CFTR) potentiator and a CFTR corrector. Ivacaftor helps CFTR proteins at the cell surface work better by increasing the probability opening of the protein channels. Tezacaftor increases the number of CFTR proteins that reach the cell surface. As a result, IVA/TEZ permits more chloride ions to move across the cell membrane and helps to maintain salt and water balance in certain organs.

In patients with the homozygous F508del mutation, IVA/TEZ demonstrated improvements in percent predicted forced expiratory volume in 1 second (FEV_1) vs. placebo (treatment difference = 4%, $p < 0.0001$). In addition, the number of pulmonary exacerbations through week 24 was less with IVA/TEZ vs. placebo (78 events vs. 122 events, $p = 0.0054$).

However, in patients with heterozygous F508del mutations, the benefit over IVA alone was modest (6.8% vs. 4.7%; treatment difference = 2.1%, $p < 0.0001$).

The most common adverse events reported in the trials were infective pulmonary exacerbation, cough, headache, nasopharyngitis, and increased sputum.

In the trials, IVA/TEZ was given orally once daily in the morning, followed by IVA alone each evening.

- CFTR potentiator/CFTR corrector combination
- Homozygous F508del patients: 4% greater improvement in FEV_1 vs. placebo
- Heterozygous F508del mutations: 2.1% greater improvement in FEV_1 vs. IVA alone
- Common adverse events: infective pulmonary exacerbation, cough, headache, nasopharyngitis, and increased sputum
- Dose: IVA/TEZ orally each morning, followed by IVA alone each evening

Continued…

ivacaftor/tezacaftor (continued...)

Competitive environment

IVA/TEZ offers another oral treatment option for CF patients with specific CFTR mutations. In addition, unlike Orkambi® (lumacaftor/ivacaftor), IVA/TEZ is touted as having a reduced risk for bronchoconstriction. As many as 20 – 30% of homozygous F508del patients discontinue Orkambi due to adverse events, such as bronchoconstriction.

However, the overall benefit of TEZ appears to be modest. The pivotal trial in patients with homozygous F508del mutations did not compare IVA/TEZ to Orkambi, which would have provided a more useful comparison than to placebo. Also, based on trial protocols, patients with heterozygous F508del will still require IVA as an evening dose. Thus, twice daily dosing is required.

At this time, IVA/TEZ is being pursued for patients < 12 years of age. In contrast, Orkambi is approved for patients ≥ 6 years old with homozygous F508del mutation in the CFTR gene.

For reference, the annual WAC for Kalydeco is approximately $311,000.

- Advantages: oral, offers another treatment option, may have reduced risk for bronchoconstriction
- Disadvantages: moderate benefit in trials, separate evening dose of ivacaftor alone required in heterozygous F508del patients
- Annual WAC for Kalydeco ~$311,000.

Expected FDA decision date

IVA/TEZ was granted breakthrough and orphan drug designations.

IVA/TEZ was also granted a priority review. An FDA decision regarding the approval of IVA/TEZ is expected by February 28, 2018.

- Orphan drug
- Breakthrough status
- Priority review
- PDUFA: 2/28/2018

netarsudil mesylate (Rhopressa)

Manufacturer: Aerie Pharmaceuticals

Therapeutic use

Netarsudil is in development for the treatment of open-angle glaucoma and ocular hypertension.

- Treatment of open-angle glaucoma and ocular hypertension

Clinical profile

Netarsudil is a rho kinase and norepinephrine transporter antagonist. It is thought to lower intraocular pressure (IOP) by three MOAs: increasing fluid outflow through the ocular drainage pathway, reducing ocular fluid production, and directly reducing episcleral venous pressure. In addition, pharmacokinetic studies suggest that systemic absorption is minimal.

In trials, netarsudil was found to be non-inferior to timolol at reducing IOP. However, statistically significant improvement was only achieved in a subset of patients whose baseline IOP was < 25 mmHg. In fact, in one of the trials, patients with IOP levels < 27 mmHg failed to meet the non-inferiority endpoint vs. timolol.

The common adverse events reported in the trials included conjunctival hyperemia, conjunctival hemorrhage, eyelid erythema, blurry vision, and corneal deposits.

Netarsudil is administered ophthalmically once daily.

- Rho kinase/norepinephrine transporter antagonist
- Ophthalmic formulation
- Non-inferior to timolol in patients with baseline IOP < 25 mmHg
- Common AEs: conjunctival hyperemia, conjunctival hemorrhage, eyelid erythema, blurry vision, corneal deposits
- Dose: once daily to affected eyes

Competitive environment

Netarsudil uses a novel MOA and offers another treatment alternative for patients with glaucoma and ocular hypertension.

However, netarsudil was only found to be non-inferior to timolol in a subset of patients. In addition, in one trial as many as 20% of patients saw a loss of efficacy over time. High rates of conjunctival hyperemia also occurred in some trials. Further, if approved, netarsudil will be entering a highly competitive market.

The average monthly WAC for glaucoma medications is approximately $200.

- Advantages: novel MOA, offers another treatment option
- Disadvantages: only achieved non-inferiority to timolol, up to 20% lost efficacy in one trial, high rates of conjunctival hyperemia, competitive market
- Average monthly WAC for glaucoma drugs ~ $200

Expected FDA decision date

An FDA decision regarding the approval of netarsudil is expected by February 28, 2018.

- PDUFA: 2/28/2018

pegvaliase (Peg-Pal)

Manufacturers: BioMarin/Merck

Therapeutic use

Pegvaliase is in development to reduce blood phenylalanine (Phe) levels in adults with phenylketonuria (PKU) who have uncontrolled blood Phe levels on existing management.

PKU is a rare genetic disease resulting in the build-up of Phe in the blood and tissues. PKU leads to developmental delays in children and has behavioral, emotional, and social impacts for these patients. In many cases, patients exhibit microencephaly with corresponding cognition and intellectual disability.

PKU affects approximately 1 in 10,000 to 15,000 newborns.

- To reduce blood Phe levels in adults with PKU who have uncontrolled blood Phe levels on existing management

Clinical profile

Pegvaliase is a form of enzyme replacement therapy. Pegvaliase is a pegylated recombinant phenylalanine ammonia lyase, an enzyme that acts to reduce Phe levels and prevents its accumulation in the body.

In trials, patients exhibited a 34.7% – 62% improvement in Phe levels from baseline. Moreover, in one trial 79% of patients achieved at least a 20% reduction in Phe levels from baseline.

The common adverse events reported in trials included arthralgia, headache, fatigue, anxiety, attention disturbance, injection site reaction, nasopharyngitis, nausea, itching, and rash.

Based on the trials, pegvaliase is administered SC once daily.

- Enzyme replacement
- SC formulation
- Up to 62% reduction in Phe levels from baseline
- Common adverse events: arthralgia, headache, fatigue, anxiety, attention disturbance, injection site reaction, nasopharyngitis, nausea, itching, and rash
- Dose: once daily

Competitive environment

Pegvaliase offers a new approach to treating PKU. Currently, Kuvan is the only FDA-approved pharmaceutical treatment for PKU, thus treatment options are very limited, especially in patients who are inadequately managed on Kuvan.

While pegvaliase requires SC administration, BioMarin and Merck are developing pegvaliase as a self-administered injectable.

For reference, the average monthly WAC for Kuvan is ~$9,300.

- Advantages: novel MOA, limited treatment options for PKU
- Disadvantage: requires SC (but may be self-administered)
- Average monthly WAC for Kuvan ~$9,300

Expected FDA decision date

Pegvaliase was granted an orphan drug designation by the FDA.

An FDA decision regarding the approval of pegvaliase is expected by late May 2018.

- Orphan drug
- PDUFA: 5/2018

OptumRx brand pipeline forecast

OptumRx closely monitors and evaluates the pipeline landscape for upcoming brand drug approvals, including both traditional and specialty medications. This report provides a summary of developmental drugs that may be approved in the upcoming two years.

Read more

OptumRx generic pipeline forecast

OptumRx closely monitors and evaluates the pipeline landscape for upcoming first-time generics and biosimilars. This report provides a summary of upcoming first-time generic drugs and biosimilars that may be approved in the upcoming two years.

Read more

Getting acquainted with pipeline forecast terms

Clinical trial phases

Phase I trials	Researchers test an experimental drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
Phase II trials	The experimental study drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
Phase III trials	The experimental study drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.
Phase IV trials	Post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Pipeline acronyms

ANDA	Abbreviated New Drug Application
BLA	Biologic License Application
CRL	Complete Response Letter
FDA	Food and Drug Administration
NME	New Molecular Entity
NDA	New Drug Application
sBLA	Supplemental Biologic License Application
sNDA	Supplemental New Drug Application
OTC Drugs	Over-the-Counter Drugs
PDUFA	Prescription Drug User Fee Act
REMS	Risk Evaluation and Mitigation Strategy

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