OPTUMRx®

RxOutlook®

1st Quarter 2019

RxOutlook® is a quarterly report that summarizes the latest pipeline drug information, trend news, upcoming generic launches, and emerging therapies in today's pharmaceutical market.

The report includes:

Detailed insights (eg, therapeutic use, clinical profile, competitive environment and regulatory timeline) for key pipeline drugs with potential FDA approvals within the 1st or 2nd quarter.

- Summary of upcoming brand drug approvals, including traditional and specialty medications.
- Summary of upcoming first-time generics and biosimilars.
- Summary of key pending new indications.

Key topics in this quarter's edition include:

- Esketamine for treatment-resistant depression
- Onasemnogene abeparvovec (Zolgensma) for the treatment of spinal muscular atrophy type 1
- NKTR-181 for the treatment of chronic low back pain.

Pending drug approvals*

Drug Name	Manufacturer	Indication/Use	Expected FDA Decision Date
esketamine	Janssen	Treatment-resistant depression	3/4/2019
metoclopramide nasal spray (Gimoti)	Evoke Pharma	Diabetic gastroparesis	4/1/2019
selinexor	Karyopharm Therapeutics	Multiple myeloma	4/5/2019
dolutegravir/lamivudine	ViiV Healthcare	HIV-1 infection	4/18/2019
risankizumab	AbbVie/Boehringer Ingelheim	Plaque psoriasis	4/25/2019
onasemnogene abeparvovec (Zolgensma)	Novartis	Spinal muscular atrophy	5/2019
quizartinib	Daiichi Sankyo	Acute myeloid leukemia	5/25/2019
NKTR-181	Nektar Therapeutics	Chronic low back pain	5/28/2019
celiprolol (Edsivo)	Acer Therapeutics	Vascular Ehlers-Danlos syndrome	6/25/2019

*Key pipeline drugs with FDA approval decisions expected in the 1st or 2nd quarter 2019.

Esketamine

Manufacturer: Janssen

Therapeutic use

Esketamine is in development for the treatment of adult patients with treatment-resistant major depressive disorder (MDD).

- Treatment of adult patients with treatment-resistant MDD

Clinical profile

Intravenously administered ketamine is an anesthetic drug that in more recent years has been used off-label for treatment-resistant depression. Ketamine is an N-methyl-D-aspartate (NMDA) antagonist, or glutamate receptor modulator, and it's believed to work by restoring synaptic connections in the brain cells in patients with depression. Esketamine is the S-enantiomer of ketamine, which binds more potently to the NMDA receptor than the other ketamine stereoisomer, and it is formulated for intranasal administration. The safety and efficacy of esketamine was evaluated in five trials of esketamine in patients with treatment-resistant MDD: three short-term trials; one withdrawal maintenance of effect trial; and one long-term safety trial.

In one short-term (4-week) pivotal trial, esketamine provided a statistically significant improvement in the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score vs. placebo at day 28. The least-squares mean difference was -4.0 (95% CI: -7.31, -0.64; p = 0.010). However, in the other two short-term trials, esketamine failed to achieve the primary endpoint. In the withdrawal maintenance trial, esketamine provided a delayed time to relapse beyond 16 weeks. The risk of relapse was 51% lower with esketamine vs. placebo.

The most common adverse events (AEs) in the trials were dizziness, nausea, dissociation, headache, and increased blood pressure.

Esketamine is administered intranasally twice weekly during induction therapy and may be administered once weekly for maintenance therapy.

- NMDA receptor antagonist
- Intranasal formulation
- Mixed efficacy data: Of the 3 short-term pivotal trials, esketamine met the primary endpoint of improvement in depressive symptoms in only 1 trial.
- Delayed time to relapse beyond 16 weeks vs. placebo in a withdrawal maintenance trial
- Common AEs: dizziness, nausea, dissociation, headache, and increased blood pressure
- Dose: twice weekly (induction); once weekly (maintenance)

Esketamine (continued...)

Competitive environment

Esketamine would offer a novel mechanism of action (MOA) for the treatment of MDD. Treatment-resistant depression is a large market, with about one-third of patients not responding to conventional antidepressant therapies. The esketamine maintenance dose may also be administered just once weekly.

Due to safety concerns and risk of misuse and abuse, esketamine will likely require administration in healthcare settings where the patient could be monitored for 2 hours after administration and the drug would not be dispensed directly to patients. Esketamine will require DEA scheduling as a controlled substance (the chemically similar ketamine is classified as a C-III substance). Esketamine also demonstrated mixed efficacy in the short-term pivotal trials.

Alternative options are available for treatment of MDD, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and atypical antipsychotics. Many of the agents in these classes are available generically and none are classified as controlled substances.

For reference, the WAC for Rexulti® (brexpiprazole), a branded atypical antipsychotic indicated for adjunctive therapy of depression, is approximately $1,100 per 30 days.

- Advantages: novel MOA for the treatment of MDD, potential large market, once weekly maintenance dosing
- Disadvantages: administration in a healthcare setting, DEA scheduling, mixed efficacy, generic alternatives available
- WAC for Rexulti is ~$1,100 per 30 days

Expected FDA decision date

An FDA Advisory Committee will discuss esketamine on February 12, 2019 and an FDA approval decision is expected by March 4, 2019.

The FDA granted breakthrough therapy and fast track designations to esketamine.

- PDUFA: 3/4/2019
- Breakthrough status
- Fast track status

Metoclopramide nasal spray (Gimoti)

Manufacturer: Evoke Pharma

Therapeutic use

Intranasally administered metoclopramide is in development for relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.

Diabetic gastroparesis is a gastrointestinal (GI) disorder in which the stomach takes too long to empty its contents resulting in serious digestive system symptoms. The gastric delay caused by gastroparesis can compromise absorption of orally administered medications.

Currently, oral and injectable formulations of metoclopramide are available for the treatment of diabetic gastroparesis.

- Relief of symptoms in adult women with acute and recurrent diabetic gastroparesis

Clinical profile

Metoclopramide is a dopamine-2 receptor antagonist. In the treatment of gastroparesis, metoclopramide is believed to work by enhancing the response to acetylcholine in tissue of the upper GI tract, which causes enhanced motility and accelerated gastric emptying without stimulating gastric, biliary, or pancreatic secretions.

In addition to a bioequivalence trial to oral metoclopramide tablets, an efficacy trial of intranasal metoclopramide was evaluated vs. placebo in adult women with diabetic gastroparesis. The trial failed to achieve the primary endpoint in the overall population; however, statistical superiority was met for improvement in symptom score, nausea, and abdominal pain in the subset of patients with moderate to severe gastroparesis.

The most common AEs reported in the trials were headache, fatigue, and nasal irritation; metoclopramide products are also associated with tardive dyskinesias, although this was not observed in the trials for intranasal metoclopramide.

In the trials, metoclopramide was administered intranasally four times a day (30 minutes before each meal and once before bedtime).

- Dopamine-2 receptor antagonist
- Intranasal formulation
- Improved symptom score, nausea, and abdominal pain vs. placebo in patients with moderate to severe gastroparesis
- Common AEs: headache, fatigue, and nasal irritation
- Safety: tardive dyskinesias
- Dose: four times a day

Competitive environment

If approved, intranasal metoclopramide would provide a novel formulation for the administration of metoclopramide. An intranasal formulation would bypass the GI tract which could be beneficial in patients with gastroparesis. While the proposed indication is limited to women, gastroparesis disproportionally affects adult women.

However, intranasal metoclopramide only demonstrated efficacy in a subset of patients (moderate-to-severe gastroparesis) in a clinical trial vs. placebo. Intranasal metoclopramide will need to be administered four times a day and generic alternatives are available. In addition, there are no head-to-head trials comparing intranasal metoclopramide with oral liquid formulations. Oral liquid formulations are commonly used in patients with gastroparesis.

- Advantages: novel formulation, bypasses GI tract
- Disadvantages: administered four times daily, availability of generic alternatives of oral metoclopramide, lack of head-to-head data comparing intranasal metoclopramide vs. oral liquid formulations

Expected FDA decision date

An FDA approval decision is expected by April 1, 2019.

- PDUFA: 4/1/2019

Selinexor

Manufacturer: Karyopharm Therapeutics

Therapeutic use

Selinexor is in development for the treatment of patients with penta-refractory multiple myeloma.

Multiple myeloma is a cancer of the plasma cells (white blood cells that produce antibodies). There are about 32,000 new cases expected to be diagnosed in 2019 and about 13,000 deaths are expected to occur. Almost all patients with multiple myeloma who survive initial treatment will eventually relapse and require further therapy. The 5-year survival rate is approximately 50%.

- Treatment of patients with penta-refractory multiple myeloma

Clinical profile

Selinexor is a first-in-class selective nuclear export (SINE) compound inhibitor. Selinexor inhibits the nuclear export protein XPO1, leading to the accumulation of tumor suppressor proteins in the cell nucleus. This reinitiates and amplifies their tumor suppressor function and is believed to lead to the selective induction of apoptosis in cancer cells, while largely sparing normal cells.

Selinexor was evaluated in a single-arm, early stage trial in patients with refractory multiple myeloma. Participants in the trial had tried a median of seven prior regimens. Selinexor provided an overall response rate (ORR) of 26.2%. In addition, median progression-free survival (PFS) was 3.7 months and median OS was 8.6 months.

The most common AEs in the trial were cytopenias, nausea, fatigue, and weight loss.

In the trial, selinexor was administered orally twice weekly.

- SINE compound inhibitor
- Oral formulation
- ORR = 26.2%; PFS = 3.7 months; OS = 8.6 months
- Common AEs: cytopenias, nausea, fatigue, weight loss
- Dose: twice weekly

Competitive environment

Selinexor is administered orally twice weekly and would provide a novel MOA for the treatment of multiple myeloma. If approved, selinexor would be the first approved treatment for penta-refractory multiple myeloma. Selinexor is also being studied for numerous other indications, including earlier line therapy in the treatment of multiple myeloma.

Other drugs approved for multiple myeloma include: Darzalex® (daratumumab), Empliciti® (elotuzumab), Kyprolis® (carfilzomib), Pomalyst® (pomalidomide), Revlimid® (lenalidomide), and Velcade® (bortezomib).

The initial proposed indication for selinexor is narrow, with patients likely needing to fail most other treatment options before transitioning to selinexor. In addition, the data available is from an early stage trial, although the strength of the results suggests likely approval.

- Advantages: oral, twice weekly, novel MOA, potential first approved product for penta-refractory multiple myeloma
- Disadvantages: narrow initial indication, lack of late stage trial data

Expected FDA decision date

An FDA Advisory Committee meeting is scheduled in the 1st quarter of 2019 (date has not yet been announced).

An FDA approval decision is expected by April 5, 2019.

The FDA granted fast track and orphan drug designations to selinexor.

- FDA Advisory Committee meeting: 1st Qtr 2019
- PDUFA: 4/5/2019
- Fast track status
- Orphan drug status

dolutegravir/lamivudine

Manufacturer: ViiV Healthcare

Therapeutic use

Dolutegravir/lamivudine is in development for the treatment of human immunodeficiency virus (HIV)-1 infection in treatment-naïve patients.

- Treatment of HIV-1 infection in treatment-naïve patients

Clinical profile

Dolutegravir is an HIV integrase strand transfer inhibitor and lamivudine is a nucleoside reverse transcriptase inhibitor (NRTI). Currently, dolutegravir and lamivudine are available as single-ingredient products, and they are both included as part of other fixed-dose combination products (e.g., Triumeq® [abacavir/ dolutegravir/ lamivudine]).

In two pivotal trials, the efficacy of dolutegravir/lamivudine was compared with Tivicay® (dolutegravir) plus Truvada® (tenofovir/emtricitabine) in treatment-naïve, HIV-1 infected patients. The primary endpoint was virologic suppression, defined as the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48. Virologic suppression was achieved in 91% (655/716) of patients in the dolutegravir/ lamivudine arm vs. 93% (669/717) with Tivicay plus Truvada (difference -1.7%; 95% CI: -4.4 to 1.1); non-inferiority criteria were met.

The most common AEs in the trials were headache, diarrhea, nasopharyngitis, upper respiratory tract infection, nausea, and insomnia.

In the trials, dolutegravir/lamivudine was administered orally once daily.

- Dolutegravir: integrase strand transfer inhibitor; lamivudine: NRTI
- Oral formulation (fixed-dose combination)
- Non-inferior to Tivicay plus Truvada virological efficacy
- Common AEs: headache, diarrhea, nasopharyngitis, upper respiratory tract infection, nausea, and insomnia
- Dose: once daily

Competitive environment

Dolutegravir/lamivudine is an oral fixed-dose combination given once daily. In the pivotal trials, the two-drug regimen was shown to be non-inferior to a commonly used first-line, three-drug HIV regimen. The only other FDA-approved two-drug complete HIV regimen is Juluca™ (dolutegravir/rilpivirine, also by ViiV). Dolutegravir is considered a preferred integrase strand transfer inhibitor with good tolerability and a high barrier to resistance.

Resistance is always a concern with new HIV drug regimens, particularly a two-drug regimen; however, treatment-emergent resistance did not appear to be an issue in the pivotal trials. A three-drug regimen is considered first-line therapy according to treatment guidelines and there likely would be a slow uptake for this fixed-dose combination unless the combination gets recommended status in the guidelines. Currently, the combination of dolutegravir and lamivudine is listed as an alternative in the treatment guidelines for patients who cannot use recommended three-drug regimens.

Finally, there are several other alternative fixed-dose combinations for the treatment of HIV-1 infection.

For reference, the WAC for Juluca is approximately $33,000 per year.

- Advantages: oral, once daily, complete two-drug HIV regimen, dolutegravir is a preferred integrase strand transfer inhibitor
- Disadvantages: concerns about long-term emergence of resistance, three-drug regimens are standard of care, alternative fixed-dose combinations available
- WAC for Juluca is ~$33,300 per year

Expected FDA decision date

An FDA approval decision is expected by April 18, 2019.

- PDUFA: 4/18/2019

risankizumab

Manufacturers: AbbVie/Boehringer Ingelheim

Therapeutic use

Risankizumab is in development for the treatment of patients with moderate to severe plaque psoriasis.

- Treatment of patients with moderate to severe plaque psoriasis

Clinical profile

Risankizumab is an interleukin-23 (IL-23) inhibitor. IL-23 is a key cytokine involved in inflammatory processes and is thought to be linked to a number of chronic immune-mediated diseases.

In the four pivotal trials, risankizumab met key co-primary and key secondary endpoints vs. placebo, Humira® (adalimumab), and Stelara® (ustekinumab) across four pivotal trials. At 12 weeks, PASI 90, defined as at least 90% improvement in Psoriasis Area and Severity Index, was achieved in 72% to 75% of patients treated with risankizumab vs. 42% to 48% with Humira or Stelara. A static physician global assessment (sPGA) score of clear/almost clear was achieved at 12 weeks in 84% to 88% of patients treated with risankizumab vs. 60% to 63% with Humira or Stelara.

The most common AEs in the trials were upper respiratory tract infection and diarrhea.

In the clinical trials, the maintenance dose for risankizumab was administered every 12 weeks subcutaneously (SC).

- IL-23 inhibitor
- SC formulation
- Statistically significant improvement in the PASI 90 and sPGA score vs. placebo, Humira, and Stelara
- Common AEs: upper respiratory tract infection and diarrhea
- Dose: every 12 weeks (maintenance dose)

Competitive environment

If approved, risankizumab would add another option to the treatment armamentarium for plaque psoriasis, a market that is becoming increasingly crowded. It demonstrated statistical superiority vs. active controls (Humira, Stelara) and can be administered every 12 weeks.

If approved, risankizumab would be the third IL-23 inhibitor to enter the market, joining competitors Tremfya® (guselkumab) and Ilumya™(tildrakizumab-asmn). In addition, alternatives outside of the IL-23 inhibitor class are also available (eg, Cosentyx® [secukinumab]).

For reference, the WAC for Tremfya (every 8 weeks) is ~$10,850 and Ilumya (every 12 weeks) is ~$13,250.

- Advantages: another treatment option, demonstrated statistical superiority vs. Humira and Stelara, administered every 12 weeks
- Disadvantages: competition within class and alternative MOAs for treatment of plaque psoriasis, late market entry
- WAC for Tremfya (every 8 weeks) is ~$10,850; Ilumya (every 12 weeks) is ~$13,250

Expected FDA decision date

An FDA approval decision is expected by April 25, 2019.

- PDUFA: 4/25/2019

onasemnogene abeparvovec (Zolgensma)

Manufacturer: Novartis

Therapeutic use

- Treatment of SMA type 1

Onasemnogene abeparvovec is in development for the treatment of spinal muscular atrophy (SMA) type 1.

SMA is a rare group of severe neuromuscular disorders characterized by the loss of motor neurons leading to progressive muscle weakness and atrophy. SMA is caused by a genetic defect in the SMN1 gene, which is responsible for coding a protein necessary for survival of motor neurons. The defect leads to deficient or dysfunctional SMN protein, and the symptoms of muscle weakness. The incidence of SMA is approximately one in 10,000 live births yet is the leading genetic cause of infant mortality.

A severe form of SMA is type 1, which can develop at birth or the first few months of life. SMA type 1 leads to mortality or the need for permanent ventilation support by 24 months of age for more than 90% of patients.

Clinical profile

- Gene therapy
- IV formulation
- After 24 months of follow-up, 15 of 15 patients were alive and without the need for permanent ventilation
- Common AE: elevated liver transaminases
- Dose: one-time infusion

Onasemnogene abeparvovec is a novel gene therapy, which uses a non-replicating adeno-associated virus capsid to deliver a functional copy of a human SMN gene to the patient's own cells.

In an early stage trial, 15 of 15 (100%) patients were alive and without need for permanent ventilation after 24 months of follow-up. Additionally, 11 of 12 (92%) patients who received the proposed therapeutic dose could sit unassisted for ≥ 5 seconds. Preliminary data from an ongoing late stage trial support the positive findings from the early stage trial.

The most common AE in the trials was elevated liver transaminases.

In the trials, onasemnogene abeparvovec was administered as a one-time IV infusion.

onasemnogene abeparvovec (Zolgensma) (continued)

Competitive environment

If approved, onasemnogene abeparvovec would provide a novel MOA (gene therapy) for the treatment of SMA type 1. The only other FDA-approved drug for SMA is Spinraza® (nusinersen). Onasemnogene abeparvovec is administered as a one-time infusion, whereas Spinraza requires chronic intrathecal dosing. While final data is unavailable from the late stage trial, the results from the early stage trial are promising.

However, there is a lack of long-term data with onasemnogene abeparvovec and providers and patients may want to use Spinraza following administration of the one-time infusion with onasemnogene abeparvovec.

The projected cost of the one-time infusion of onasemnogene abeparvovec is over $2 million per patient.

- Advantages: novel MOA, one-time infusion for potentially long-term benefits (vs. chronic intrathecal dosing with Spinraza), promising early stage data
- Disadvantages: lack of long-term data, providers and patients may still want to use Spinraza following onasemnogene abeparvovec, IV administration
- Projected cost is over $2 million

Expected FDA decision date

An FDA approval decision is expected in May 2019.

The FDA granted breakthrough therapy, fast track, and orphan drug designations to onasemnogene abeparvovec.

- PDUFA: 5/2019
- Breakthrough status
- Fast track status
- Orphan drug status

quizartinib

Manufacturer: Daiichi Sankyo

Therapeutic use

Quizartinib is in development for the treatment of adult patients with relapsed or refractory FLT3-ITD acute myeloid leukemia (AML).

AML is a rapidly progressing cancer that crowds out normal cells in the bone marrow and bloodstream, resulting in low numbers of normal blood cells and a continuous need for transfusions. The National Cancer Institute estimated that approximately 19,520 people were diagnosed with AML in 2018; approximately 10,670 patients with AML are estimated to have died of the disease in 2018.

Approximately 25 to 30% of patients with AML have a mutation in the FLT3 gene.

- Treatment of adult patients with relapsed or refractory FLT3-ITD AML

Clinical profile

Quizartinib is a kinase inhibitor with selective FLT3 inhibition activity.

In the pivotal trial, quizartinib was compared with salvage chemotherapy in patients with relapsed or refractory FLT3-ITD mutated AML. Overall survival (OS) was 6.2 months with quizartinib vs. 4.7 months with salvage chemotherapy ($p = 0.0177$).

The composite complete remission rate (includes patients with complete remission, complete remission with incomplete platelet recovery, and complete remission with incomplete hematological recovery) was 48% with quizartinib vs. 27% with salvage chemotherapy ($p = 0.0001$) and the stem cell transplant rate was 32% vs. 12%, respectively ($p < 0.0001$).

The most commonly reported AEs included infections, bleeding, nausea, pyrexia, febrile neutropenia, and vomiting.

In the trial, quizartinib was administered orally once daily.

- Selective FLT3 inhibitor
- Oral formulation
- OS = 6.2 months vs. 4.7 months with salvage chemotherapy; higher rates of response and stem cell transplant vs. salvage chemotherapy
- Common AEs: infections, bleeding, nausea, pyrexia, febrile neutropenia, and vomiting
- Dose: once daily

Competitive environment

If approved, quizartinib would add another oral option in the treatment armamentarium for patients with AML and a FLT3 mutation. Currently, Rydapt® (midostaurin) is the only FDA-approved targeted therapy for untreated AML patients with a FLT3 mutation. Xospata™ (gilteritinib) is also approved for the treatment of relapsed or refractory AML patients with a FLT3 mutation.

The currently proposed indication for quizartinib is limited to patients with relapsed or refractory FLT3-ITD mutated AML. In addition, modest improvement in OS was demonstrated vs. salvage chemotherapy and there are no head-to-head data comparing the different FLT3 inhibitors.

For reference, the WAC for Xospata is $22,500 per 30 days.

- Advantages: oral, once a day, another treatment option for FLT3 AML
- Disadvantages: narrow indication, modest OS benefit vs. salvage chemotherapy, no head-to-head data vs. alternative FLT3 inhibitors
- WAC for Xospata is $22,500 per 30 days

quizartinib (continued)

Expected FDA decision date

An FDA approval decision is expected by May 25, 2019.

The FDA granted breakthrough therapy, fast track, and orphan drug designations to quizartinib.

- PDUFA: 5/25/2019
- Breakthrough status
- Fast track status
- Orphan drug status

NKTR-181

Manufacturer: Nektar Therapeutics

Therapeutic use

NKTR-181 is in development for the treatment of chronic low back pain in adult patients new to opioid therapy.

- Treatment of chronic low back pain in adult patients new to opioid therapy

Clinical profile

NKTR-181 is a novel, long-acting, selective mu-opioid receptor agonist. The molecular structure of NKTR-181 is designed to have low permeability across the blood-brain barrier in order to slow the rate of drug entry into the brain to attenuate the dopamine release that underlies euphoria.

In the pivotal trial, patients achieved an average pain score reduction of over 65% (from 6.73 at screening to 2.32 at randomization [on a numeric rating scale of 0 to 10]) during the dose titration period. Average pain scores increased more in the placebo group vs. NKTR-181 at week 12 from randomization baseline (1.46 vs. 0.92, respectively, $p = 0.0019$).

NKTR-181 was also compared to immediate-release oxycodone in a human abuse potential trial. The primary endpoint was "Drug Liking", which was based on a subject-reported 100-point visual analog scale. NKTR-181 400 mg (highest efficacious dose in the pivotal efficacy trial) had a significantly lower rating of peak liking compared to oxycodone 40 and 60 mg (62.0 vs. 76.6 and 81.5; $p < 0.0001$ for both comparisons). NKTR-181 1200 mg (supratherapeutic dose) had a significantly lower rating of peak drug liking compared to oxycodone 60 mg (76.7 vs. 81.5, $p = 0.0071$); however, this dose was not statistically different from oxycodone 40 mg.

The most common AEs in the trials were nausea and constipation.

In the efficacy trial, NKTR-181 was administered orally twice a day.

- Selective mu-opioid receptor agonist
- Oral formulation
- NKTR-181 was more effective at relieving pain than placebo
- NKTR-181 demonstrated lower "Drug Liking" scores vs. immediate-release oxycodone
- Common AEs: nausea, constipation
- Dose: twice a day

Competitive environment

NKTR-181 offers another oral, long-acting opioid option for the treatment of chronic low back pain. The novel molecular structure of NKTR-181 may reduce the euphorigenic properties normally associated with opioids and in turn reduce the risk of abuse and misuse vs. conventional opioids.

However, as a mu-opioid receptor agonist, NKTR-181 will still carry a risk for addiction, misuse, and abuse and will likely require DEA scheduling. In addition, many alterative short- and long-acting opioids are currently available, including products with FDA-approved labeling for abuse-deterrence (eg, Embeda® [morphine/naltrexone], OxyContin® [oxycodone], Xtampza® ER [oxycodone]).

For reference, the WAC for Xtampza ER is approximately $500 per 30 days.

- Advantages: oral, novel molecular structure, potential reduced euphorigenic properties vs. conventional opioids
- Disadvantages: DEA scheduling, alternatives available (including products with FDA-approved labeling for abuse deterrence)
- WAC for Xtampza ER is $470 per prescription

Expected FDA decision date

The FDA granted fast track designation to NKTR-181.

An FDA approval decision is expected by May 28, 2019.

- PDUFA: 5/28/2019
- Fast track status

celiprolol (Edsivo)

Manufacturer: Acer Therapeutics

Therapeutic use

Celiprolol is in development for the treatment of vascular Ehlers-Danlos syndrome (EDS) in patients with a confirmed type III collagen mutation.

EDS is a group of inherited disorders of connective tissue. Type III collagen is found in tissues such as the skin, lungs intestinal walls, and the walls of blood vessels. Vascular EDS is the most severe subtype where patients can suffer from life threatening arterial dissections and ruptures, as well as intestinal and uterine ruptures.

Among affected people diagnosed as the result of a complication, 25% have experienced a significant medical complication by age 20 and more than 80% by age 40. The median life expectancy is 48 years.

The estimated prevalence of vascular EDS in the U.S. is about 1 in 45,000.

- Treatment of vascular EDS in patients with a confirmed type III collagen mutation

Clinical profile

Celiprolol is an oral beta1-adrenoceptor antagonist with beta2-adrenoceptor agonist action. Celiprolol is believed to work by reducing heart rate, mean pressure, and pulsatile pressure. Celiprolol may also upregulate collagen synthesis in the blood vessels.

The efficacy of celiprolol was evaluated in a European study published in 2010. In the study of 53 patients, arterial events (rupture or dissection) occurred in 20% of patients treated with celiprolol vs. 50% with placebo (hazard ratio [HR] 0.36; p = 0.040). Intestinal or uterine rupture occurred in 24% vs. 61% with placebo (HR 0.31; p = 0.01).

The most common AE in the study was fatigue.

In the study, celiprolol was administered orally twice a day.

- Beta1-adrenoceptor antagonist with beta2-adrenoceptor agonist action
- Oral formulation
- Statistically significant reduction (30% absolute risk reduction) in arterial events (rupture or dissection) and intestinal or uterine rupture vs. placebo
- Common AE: fatigue
- Dose: twice a day

Competitive environment

Celiprolol is potentially the first FDA-approved drug for the treatment of vascular EDS.

However, celiprolol does require twice a day dosing and the proposed indication is limited to a subset of patients with EDS. In addition, the efficacy supporting the FDA submission relies on a retrospective verification of data from a 2010 study. No additional efficacy trials were conducted by Acer Therapeutics.

- Advantages: oral, novel molecular entity, potential first FDA-approved option for vascular EDS
- Disadvantages: limited efficacy data, narrow indication, twice a day dosing

Expected FDA decision date

An FDA approval decision is expected by June 25, 2019.

The FDA granted orphan drug designation to celiprolol.

- PDUFA: 6/25/2019
- Orphan drug status

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

OptumRx key pending indications

OptumRx closely monitors and evaluates the pipeline landscape for pending new indications for existing medications. This report provides a summary of key pending new indications that may be approved in the upcoming year.

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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