OPTUMRx®

RxOutlook®

2nd Quarter 2016

Pending drug approvals

Drug name	Manufacturer	Indication/use	Expected FDA decision date
latanoprostene bunod (Vesneo™)	Bausch & Lomb/Nicox	Open angle glaucoma/ocular hypertension	7/21/2016
bezlotoxumab	Merck/Bristol-Myers Squibb	Prevention of *Clostridium difficile* infection recurrence	7/23/2016
insulin degludec/liraglutide (Xultophy®)	Novo Nordisk	Type 2 diabetes mellitus	7/25/2016
lorcaserin extended-release (Belviq XR™)	Arena/Eisai	Obesity	7/2016
ombitasvir/paritaprevir/ritonavir; dasabuvir (Viekira Pak™)	AbbVie/Enanta	Hepatitis C	8/2016
andexanet alfa	Portola	Factor Xa inhibitor antidote	8/17/2016
etelcalcetide (Parsabiv™)	Amgen/Ono	Secondary hyperparathyroidism	8/24/2016
atezolizumab	Genentech	Bladder cancer, non-small cell lung cancer	9/2016 - 10/2016
canagliflozin/metformin extended release (Invokamet® XR)	Janssen	Type 2 diabetes mellitus	9/20/2016

latanoprostene bunod (Vesneo)

Manufacturers: Bausch & Lomb/Nicox

Therapeutic use
Vesneo is in development for the treatment of primary open angle glaucoma or ocular hypertension.

- Treatment of primary open angle glaucoma/ ocular hypertension

Clinical profile
Vesneo is considered a next generation product of latanoprost (Xalatan®), made by Pfizer, which is also approved for open angle glaucoma and ocular hypertension. Similar to Xalatan, Vesneo is a prostaglandin analog, but contains an additional nitric-oxide-donating component. The nitric oxide donating component is believed to improve efficacy and safety.

In phase 3 clinical trials comparing Vesneo with timolol maleate 0.5% twice daily (BID), Vesneo was shown to be statistically superior to timolol maleate in reducing mean intraocular pressure (IOP) from baseline (-7.5 to -9.1 mmHg, $p < 0.05$).

In a phase 2b study, two of the four doses of Vesneo tested showed a greater reduction in IOP compared with latanoprost 0.005%, with a difference of approximately 1 mmHg ($p < 0.01$).

A common adverse event reported in trials was ocular redness.

Based on trial information, Vesneo will be dosed once daily.

- Nitric oxide-donating prostaglandin F2-alpha analog
- Ophthalmic formulation
- Superior to timolol in reducing IOP
- Common adverse event: ocular redness

Competitive environment
If approved, Vesneo will be the first nitric oxide-donating prostaglandin receptor agonist available for the treatment of open angle glaucoma or ocular hypertension.

However, various once daily generic alternatives are available for the treatment of open angle glaucoma and ocular hypertension (eg, latanoprost, bimatoprost).

The projected annual U.S. sales for Vesneo are $131 million by 2020.

- Advantage: novel mechanism
- Disadvantage: once daily generic alternatives are available (eg, latanoprost, bimatoprost)

Expected FDA decision date
An FDA decision regarding the approval of Vesneo is expected by July 21, 2016.

- PDUFA: 7/21/2016

bezlotoxumab

Manufacturers: Merck/Bristol-Myers Squibb

Therapeutic use
Bezlotoxumab is in development for the prevention of *Clostridium difficile (C. difficile)* infection recurrence in patients who are on standard *C. difficile* antibiotic treatment.

- Prevention of *C. difficile* infection recurrence in patients on standard *C. difficile* antibiotic treatment

Clinical profile
Bezlotoxumab is a fully human monoclonal antibody that works by neutralizing toxin B, one of the main toxins of *C. difficile* that causes inflammation and diarrhea.

In clinical trials, bezlotoxumab, given as a one-time, intravenous (IV) infusion, resulted in a significantly lower rate of *C. difficile* recurrence compared with placebo (15.7–17.4% vs. 25.7–27.6%).

There were no major safety concerns identified in the clinical trials. The most common adverse reactions were nausea, diarrhea, fever, and urinary tract infection.

Based on trial information, bezlotoxumab will be administered by a healthcare professional as a one-time, weight-based IV infusion.

- Fully human monoclonal antibody against *C. difficile* toxin B
- IV formulation
- Significantly lower rate of *C. difficile* recurrence vs. placebo
- Common adverse events: nausea, diarrhea, pyrexia, urinary tract infection

Competitive environment
Bezlotoxumab employs a novel mechanism for preventing the recurrence of *C. difficile* infection. Currently, there are no FDA-approved drugs for prevention of *C. difficile* recurrence. If approved, bezlotoxumab will be the first therapy approved for this indication.

However, bezlotoxumab will be given by IV infusion and requires healthcare provider administration. Moreover, because it is a monoclonal antibody, it is expected to be expensive.

In 2011, approximately half a million infections were caused by *C. difficile* in the U.S., with 29,000 deaths.

- Advantages: novel mechanism, no FDA-approved drugs for prevention of *C. difficile* recurrence
- Disadvantages: IV infusion, requires healthcare provider administration, high cost

Expected FDA decision date
The FDA's Antimicrobial Drugs Advisory Committee (AdCom) is scheduled to review bezlotoxumab on June 9, 2016.

The FDA granted priority review for bezlotoxumab. An FDA decision regarding the approval of bezlotoxumab is expected by July 23, 2016.

- FDA AdCom: 6/9/2016
- PDUFA: 7/23/2016

insulin degludec/liraglutide (Xultophy)

Manufacturer: Novo Nordisk

Therapeutic use

Novo Nordisk's Xultophy is being developed as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).

- Treatment of T2DM

Clinical profile

Xultophy is a combination of Tresiba® (insulin degludec), a long-acting insulin, and Victoza® (liraglutide), a glucagon-like peptide 1 (GLP-1) receptor agonist. These agents work by different mechanisms to improve glycemic control.

In one of its clinical trials, Xultophy resulted in statistically significant reductions in hemoglobin A1c (HbA1c) in comparison with insulin glargine ($p < 0.001$). Xultophy also resulted in a reduction of body weight by 1.4 kg, whereas insulin glargine resulted in an increase of 1.8 kg ($p < 0.001$). In addition, there was a 57% lower rate of hypoglycemia with Xultophy vs. insulin glargine ($p < 0.001$).

A safety signal was identified with Tresiba, which showed an increased cardiovascular (CV) risk vs. comparators. Because insulin degludec is a component of Xultophy, similar concerns may apply. Currently, the CV risk of Tresiba is being evaluated in a clinical outcomes trial. The final results are expected by the 4th quarter of 2016.

Common adverse events reported in trials with Xultophy were nausea, diarrhea, vomiting, headache, and hypoglycemia.

Based on trial information, Xultophy will be dosed once daily by subcutaneous injection.

- Long-acting insulin/GLP-1 receptor agonist
- SC formulation
- Significant reduction in HbA1c and body weight vs. insulin glargine
- Lower rate of hypoglycemia vs. insulin glargine
- Common adverse events: nausea, diarrhea, vomiting, headache, hypoglycemia

Competitive environment

The main benefit of Xultophy may be its convenience; fewer injections may be needed in those who require both a GLP-1 agonist and a long-acting insulin product.

However, there are possible CV safety concerns with insulin degludec, a component of Xultophy. Additionally, whereas long-acting insulins can be titrated up when patients require treatment intensification, due to the presence of liraglutide, there may be maximum dosage limits for Xultophy.

The projected annual U.S. sales for Xultophy are $1.7–$3 billion by 2020.

- Advantage: convenient combination of long-acting insulin/GLP-1 agonist
- Disadvantages: cardiovascular safety concerns with insulin degludec, maximum dosage limits

Expected FDA decision date

An FDA decision regarding the approval of Novo Nordisk's Xultophy is expected by July 25, 2016.

- PDUFA: 7/25/2016

lorcaserin extended-release (Belviq XR)

Manufacturers: Arena/Eisai

Therapeutic use

Arena Pharmaceuticals, in partnership with Eisai, is developing a once daily extended-release Belviq tablet, as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients, based on initial body mass index (BMI).

Immediate-release Belviq is currently available and is indicated for use in adults with BMI ≥ 30 kg/m^2, or BMI ≥ 27 kg/m^2 with at least one weight-related comorbid condition, such as hypertension, T2DM, or dyslipidemia.

- An adjunct to a reduced calorie diet and increased physical activity for chronic weight management

Clinical profile

Belviq is believed to decrease food consumption and promote satiety by activating serotonin 5-HT$_{2C}$ receptors in the brain.

The results from bioequivalence studies comparing Belviq XR to immediate-release Belviq are still pending.

Common adverse events are expected to be similar to immediate-release Belviq.

Immediate-release Belviq is dosed twice daily (BID). In contrast, Belviq XR will be dosed once daily.

- Serotonin 5-HT$_{2C}$ receptor agonist
- Oral formulation
- Common adverse events: similar to immediate-release Belviq

Competitive environment

Unlike immediate-release Belviq, Belviq XR offers a once daily dosing option to patients.

However, there are other once daily dosing options available for obesity treatment, such as Qsymia® and phentermine.

The current wholesale acquisition cost (WAC) of immediate-release Belviq is approximately $102.50 per month, with worldwide sales of $51 million in 2014.

- Advantage: once daily dosing option
- Disadvantage: other options available

Expected FDA decision date

An FDA decision regarding the approval of Belviq XR is expected by July 2016.

- PDUFA: 7/2016

ombitasvir/paritaprevir/ritonavir; dasabuvir (Viekira Pak)

Manufacturers: AbbVie/Enanta

Therapeutic use

AbbVie, in partnership with Enanta, is developing a once daily Viekira Pak formulation.

Currently, Viekira Pak is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection: genotype 1b without cirrhosis or with compensated cirrhosis, and genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

The current dosing of Viekira Pak is one fixed-dose tablet containing ombitasvir, paritaprevir and ritonavir taken once daily, and a dasabuvir tablet taken twice daily.

- Treatment of patients with genotype 1 chronic HCV infection

Clinical profile

Viekira Pak combines a CYP3A inhibitor (ritonavir) that increases the plasma concentration of paritaprevir and 3 direct-acting antiviral agents with differing mechanisms of action against genotype 1 HCV: an NS5A inhibitor (ombitasvir), an NS3/4A protease inhibitor (paritaprevir), and an NS5B polymerase inhibitor (dasabuvir).

The results from bioequivalence studies comparing once daily Viekira Pak and the existing Viekira Pak formulation are pending.

Common adverse events will likely be similar to the existing Viekira Pak.

- NS5A inhibitor/ NS3/4A protease inhibitor/ CYP3A inhibitor and NS5B polymerase inhibitor
- Once-daily oral formulation
- Common adverse events: likely similar to existing Viekira Pak

Competitive environment

The new formulation of Viekira Pak will offer a once daily dosing option to patients.

However, there are other once daily dosing options for treatment of genotype 1 chronic HCV infection, such as Harvoni® and Zepatier™. Similar to the current Viekira Pak formulation, once daily Viekira Pak will likely be contraindicated in patients with moderate and severe hepatic impairment.

The current WAC cost of the existing Viekira Pak is $83,317 and $166,635 for a 12- and 24-week treatment regimen, respectively.

- Advantage: once daily dosing
- Disadvantages: other once daily alternatives available (eg, Harvoni®, Zepatier™), likely contraindicated in moderate and severe hepatic impairment

Expected FDA decision date

An FDA decision regarding the approval of once daily Viekira Pak is expected by August 2016.

- PDUFA: 8/2016

andexanet alfa

Manufacturer: Portola

Therapeutic use
Andexanet alfa is an IV drug being developed for reversal of anticoagulant activity of direct and indirect Factor Xa inhibitors when reversal of anticoagulation is needed, such as life-threatening or uncontrolled bleeding or for emergency surgery and urgent procedures.

- Reversal of anticoagulant activity of direct and indirect Factor Xa inhibitors when reversal of anticoagulation is needed

Clinical profile
Andexanet alfa is a Factor Xa inhibitor antidote. It works by binding to Factor Xa inhibitors and preventing them from inhibiting native Factor Xa. This allows the normal hemostatic process to occur.

In clinical trials, treatment with andexanet alfa resulted in a greater reduction in anti-Factor Xa activity in healthy subjects given Eliquis® (apixaban) or Xarelto® (rivaroxaban) compared to the placebo group.

A trial in patients with acute major bleeding episodes is still ongoing.

No serious or severe adverse events were reported in the clinical trials. Treatment-related adverse events reported in trials included gastrointestinal disorders, flushing, and urticaria.

Andexanet alfa has been studied for administration as an IV bolus and as an IV bolus followed by continuous IV infusion.

- Factor Xa inhibitor antidote
- IV formulation
- Greater reduction in anti-factor Xa activity vs. placebo
- Treatment-related adverse events: gastrointestinal disorders, flushing, urticaria

Competitive environment
Currently, there are no FDA-approved drugs to reverse the activity of Factor Xa inhibitors. Thus, if approved, andexanet alfa would be the first Factor Xa inhibitor antidote.

However, the completed pivotal trials were based on healthy volunteers and only examined the impact on anti-Factor Xa activity. Moreover, the risk for thrombosis remains unknown.

The projected annual U.S. sales for andexanet alfa are $218 million by 2020.

- Advantage: first Factor Xa inhibitor antidote
- Disadvantages: clinical studies were based on healthy volunteers, unknown risk of thrombosis

Expected FDA decision date
The FDA granted andexanet alfa an orphan drug designation and breakthrough status. An FDA decision regarding the approval of Portola's andexanet alfa is expected by August 17, 2016.

- Orphan drug
- Breakthrough status
- PDUFA: 8/17/2016

etelcalcetide (Parsabiv)

Manufacturer: Amgen/Ono

Therapeutic use
Etelcalcetide is in development for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) receiving hemodialysis.

- Treatment of secondary hyperparathyroidism in patients with CKD receiving hemodialysis

Clinical profile
Etelcalcetide is an IV calcimimetic. It works by binding to and activating the calcium-sensing receptor on the parathyroid gland, thereby suppressing the secretion of parathyroid hormone (PTH).

In a clinical trial, etelcalcetide was non-inferior to Sensipar® (cinacalcet), measured as the achievement of greater than 30% reduction from baseline in mean pre-dialysis serum intact PTH levels.

Common adverse events reported in trials include reduction in serum calcium, diarrhea, nausea, vomiting, and symptomatic hypocalcemia.

Based on trial information, Parsabiv will be dosed three times weekly with each dialysis session.

- Calcimimetic
- IV formulation
- Common adverse events: reduction in serum calcium, diarrhea, nausea, vomiting, symptomatic hypocalcemia

Competitive environment
If approved, Parsabiv will be the first IV calcimimetic. Thus, it may also be a suitable option in patients unable to tolerate oral therapy.

However, alternatives are available including generically available products, such as calcitriol, doxercalciferol, and paricalcitol. An oral calcimimetic option is also available (ie, Sensipar).

The projected annual U.S. sales for Parsabiv are $135 million by 2020.

- Advantage: first IV calcimimetic, an option for patients unable to tolerate oral therapy
- Disadvantage: other options available (eg, Sensipar)

Expected FDA decision date
An FDA decision regarding the approval of Parsabiv is expected by August 24, 2016.

- PDUFA: 8/24/2016

atezolizumab

Manufacturer: Genentech

Therapeutic use
Genentech's atezolizumab is an IV drug being developed for the treatment of patients with advanced or metastatic urothelial carcinoma (UC) who had disease progression during or following platinum-based chemotherapy in the metastatic setting, or whose disease worsened within 12 months of receiving platinum-based chemotherapy before or after surgery.

Atezolizumab is also in development for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease expresses the protein PD-L1 (programmed death ligand-1), as determined by an FDA-approved test, and who have progressed on or after platinum-containing chemotherapy.

- Treatment of locally advanced or metastatic UC following platinum-based chemotherapy
- Treatment of PD-L1 positive NSCLC, including patients who progressed on or after platinum-containing chemotherapy

Clinical profile
Atezolizumab is a programmed death ligand-1 (PD-L1) inhibitor. It works by binding to PD-L1 expressed on tumor cells and tumor-infiltrating immune cells, blocking its interactions with PD-1 and B7.1 receptors. By inhibiting PD-L1, atezolizumab may promote the activation of T cells.

In a phase 2 clinical trial in patients with locally advanced or metastatic UC, atezolizumab significantly improved the overall response rate (ORR) compared to historical controls (15% vs. 10%, p = 0.0058).

Similarly, in a phase 2, single-arm trial in patients with locally advanced of metastatic NSCLC, atezolizumab shrank tumors in up to 27% of patients (p = 0.0001) who had progressed on prior therapies and also expressed the highest levels of PD-L1. The median survival had not been reached at the time of the interim analysis.

Common adverse events reported in trials include fatigue, decreased appetite, fever, and anemia.

- PD-L1 (programmed death ligand-1) inhibitor
- IV formulation
- Greater ORR compared to historical controls in UC patients
- Shrank tumors in up to 27% of NSCLC patients
- Common adverse events: fatigue, decreased appetite, fever, anemia

Continued…

atezolizumab (Continued…)

Manufacturer: Genentech

Competitive environment
There are limited options available for patients with metastatic UC or PD-L1-positive NSCLC.

But while atezolizumab demonstrated some effectiveness in early trials, the pivotal phase 3 trials are still ongoing. Moreover, atezolizumab must be given by IV administration.

The projected annual U.S. sales of atezolizumab for UC are $495 million by 2020.

The projected annual U.S. sales of atezolizumab for NSCLC are $647 million by 2020.

- Advantages: effective, limited options available for treatment of UC
- Disadvantages: phase 3 trial results are pending, IV administration

Expected FDA decision date
The FDA granted breakthrough status and priority review for atezolizumab for the treatment of locally advanced or metastatic UC and for the treatment of NSCLC.

An FDA decision regarding atezolizumab's UC indication is expected by September 12, 2016.

An FDA decision regarding atezolizumab's NSCLC indication is expected by October 19, 2016.

- Priority review
- Breakthrough status

PDUFA:

- UC: 9/12/2016
- NSCLC: 10/19/2016

canagliflozin/metformin extended release (Invokamet XR)

Manufacturer: Janssen

Therapeutic use

Invokamet XR is a combination product of canagliflozin and metformin extended-release (ER), in development as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

- Treatment of T2DM

Clinical profile

The product combines a sodium-glucose transporter-2 (SGLT-2) inhibitor, canagliflozin, with an extended-release biguanide, metformin ER.

In a clinical trial, Invokamet XR resulted in a greater reduction in HbA1c compared with its individual components given alone.

The most common adverse events in trials with Invokamet XR were diarrhea, nausea, vomiting, and hypoglycemia.

Based on trial information, Invokamet XR will be dosed orally once daily.

- SGLT-2 inhibitor/biguanide
- Oral formulation
- Greater reduction in HbA1c compared with individual components alone
- Common adverse events: diarrhea, nausea, vomiting, hypoglycemia

Competitive environment

Invokamet XR will be a convenient once daily combination product of canagliflozin and metformin ER.

However, Invokamet XR is not a unique product. There are other treatment options available, including immediate-release Invokamet®, which can be given twice daily, and other similar combination products (eg, Xigduo® XR, Synjardy®).

- Advantage: once daily convenient combination product
- Disadvantage: alternatives are available (eg, Invokamet, Xigduo XR, Synjardy)

Expected FDA decision date

An FDA decision regarding the approval of Invokamet XR is expected by September 20, 2016.

- PDUFA: 9/20/2016

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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