OPTUMRx®

# RxOutlook®

3rd Quarter 2016

## Pending drug approvals

| Drug name | Manufacturer | Indication/use | Expected FDA decision date |
|---|---|---|---|
| **olaratumab** | Eli Lilly/Bristol-Myers Squibb | Soft tissue sarcoma | 9/2016–10/2016 |
| **sarilumab** | Regeneron/Sanofi | Rheumatoid arthritis | 10/30/2016 |
| **ultra fast-acting insulin aspart (FIAsp)** | Novo Nordisk | Diabetes mellitus | 10/2016 |
| **brodalumab (Siliq)** | Valeant | Plaque psoriasis | 11/16/2016 |
| **telotristat etiprate** | Lexicon/Ipsen | Carcinoid syndrome | 11/30/2016 |
| **ocrelizumab (Ocrevus™)** | Genentech | Multiple sclerosis | 12/28/2016 |
| **lutetium-177 octreotate (Lutathera®)** | Advanced Accelerator Applications/Fujifilm | Gastroenteropancreatic neuroendocrine tumors | 12/2016 |
| **solithromycin (Solithera™)** | Cempra/Toyama Chemical/Merck | Community acquired pneumonia | 12/2016 |
| **oxymetazoline** | Actavis | Rosacea | 11/2016–1/2017 |

# olaratumab

Manufacturers: Eli Lilly/Bristol-Myers Squibb

## Therapeutic use

Olaratumab is in development for use in combination with doxorubicin, for the treatment of patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery.

- In combination with doxorubicin for treatment of advanced STS not amenable to radiotherapy or surgery

## Clinical profile

Olaratumab is a platelet derived growth factor receptor-alpha (PDGFR-alpha) antagonist. PDGFR-alpha is expressed on various tumor types and plays an important role in maintaining tumor growth. Antagonizing PDGFR-alpha receptors disrupts ligand-dependent signaling in PDGFR-alpha expressing tumors.

In early-stage trials, the olaratumab arm achieved greater progression-free survival (PFS) vs. placebo (8.2 months vs. 4.4 months); however, the improvement did not reach statistical significance ($p = 0.0615$). Nonetheless, the secondary endpoint of overall survival (OS) was greater with olaratumab vs. placebo (26.5 months vs. 14.7 months; HR = 0.463, $p = 0.0003$).

The common adverse events reported in trials with olaratumab use were neutropenia, mucositis, nausea, vomiting, and diarrhea.

Olaratumab is given intravenously (IV) and dosed by weight on select days of a 21-day treatment cycle.

- PDGFR-alpha antagonist
- IV formulation
- Progression-free survival not significant vs. placebo; improved overall survival
- Common adverse events: neutropenia, mucositis, nausea, vomiting, and diarrhea

## Competitive environment

Olaratumab uses a novel mechanism of action (MOA) to treat STS, and because there are limited options for treating advanced STS, olaratumab may be a useful addition to the therapeutic armamentarium.

However, olaratumab still requires IV administration, and late-stage trial data are not available at this time.

In 2014, there were an estimated 12,000 diagnosed cases of STS in the U.S.

The projected U.S. sales are $408 million by 2020.

- Advantages: novel MOA, limited treatment options for STS
- Disadvantages: IV administration, late-stage trial data are not available
- Projected U.S. sales are $408 million by 2020

## Expected FDA decision date

Olaratumab is considered an orphan drug and was granted fast track status and priority review for STS by the FDA.

An FDA decision regarding the approval of olaratumab is expected in September or October 2016.

- Orphan drug status
- Fast track status
- Priority review
- PDUFA: 9/2016–10/2016

# sarilumab

Manufacturers: Regeneron/Sanofi

## Therapeutic use

Sarilumab is in development for the treatment of patients with active, moderate-to-severe rheumatoid arthritis (RA).

- Treatment of moderate-to-severe RA

## Clinical profile

Sarilumab is a fully human monoclonal antibody that targets the interleukin-6 (IL-6) receptor.

Actemra® (tocilizumab), which is currently available, also targets the IL-6 pathway; however, it competes with IL-6 for binding on the IL-6 receptor. In contrast, sarilumab directly antagonizes the receptor.

In trials, sarilumab was compared to placebo in patients with RA, who were taking other disease-modifying antirheumatic drugs (DMARDs) such as methotrexate. Between 56%–66.4% of patients in the sarilumab arm showed improvements in the signs and symptoms of RA vs. 33.4–34% in the placebo arm ($p < 0.0001$).

The common adverse events reported in trials with sarilumab use were infection and injection-site reactions. Reductions in neutrophil count were also observed in laboratory tests, but serious infections were uncommon.

Sarilumab is expected to be dosed by subcutaneous (SC) injection every other week.

- IL-6 receptor antagonist
- SC formulation
- Greater improvement in the signs/symptoms of RA vs. placebo
- Common adverse events: infection, injection-site reactions

## Competitive environment

Sarilumab is the first IL-6 receptor antagonist and offers another treatment option for patients with RA.

However, several treatments for RA are already available, including Actemra. In addition, Actemra IV only requires once a month dosing compared to sarilumab, which requires dosing every other week. Actemra is also indicated for polyarticular and systemic juvenile idiopathic arthritis.

The projected U.S. sales are $525 million by 2020.

- Advantages: first IL-6 receptor antagonist, another treatment option
- Disadvantages: related drug is available (ie, Actemra), requires more frequent dosing than Actemra IV
- Projected U.S. sales are $525 million by 2020

## Expected FDA decision date

An FDA decision regarding the approval of sarilumab is expected by October 30, 2016.

- PDUFA: 10/30/2016

# ultra fast-acting insulin aspart (FIAsp)

Manufacturer: Novo Nordisk

## Therapeutic use

Ultra fast-acting insulin aspart is a new formulation of insulin aspart, which is in development to improve glycemic control in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

- Treatment of T1DM and T2DM

## Clinical profile

This new formulation of insulin aspart includes L-arginine and vitamin B3 to help stabilize the insulin and assist with the speed of delivery. In contrast to standard insulin aspart, with an onset time of 15–30 minutes, this new formulation begins working within 5 minutes. Thus, it may reduce the need to pre-bolus (ie, properly time the patient's insulin injection prior to the start of a meal).

In trials, ultra fast-acting insulin aspart was shown to be non-inferior to standard insulin aspart in reducing average blood glucose levels (ie, hemoglobin A1c [HbA1c]).

The overall safety profile of this new formulation was comparable to standard insulin aspart; however, there was a higher rate of hypoglycemia within the first 2 hours after the start of a meal in T2DM patients and within the first hour after a meal in T1DM patients. But the overall risk for severe hypoglycemia was comparable to standard insulin aspart.

Because more insulin is delivered upfront with FIAsp, lower post-prandial glucose levels are expected compared to standard insulin aspart. While this benefit was observed in T1DM patients, the effect was not statistically significant in T2DM patients.

FIAsp is a mealtime insulin for SC injection.

- Ultra fast-acting insulin aspart
- SC formulation
- Non-inferior to standard insulin aspart in glycemic control
- Overall safety profile is similar to standard insulin aspart
- Higher rate of hypoglycemia within 2 hours after a meal in T2DM and 1 hour after a meal in T1DM

## Competitive environment

FIAsp offers another treatment option for diabetic patients. In addition, it may reduce the need for patients to pre-bolus, but whether this offers a meaningful clinical advantage over existing rapid-acting options is unclear at this time.

Currently, there are other rapid-acting insulins already available, including Humalog® (lispro), Novolog® (insulin aspart), and Apidra® (insulin glulisine). Furthermore, the studies were largely non-inferiority trials against standard insulin aspart.

There are an estimated 29 million diabetic patients in the U.S.

- Advantages: offers another treatment option, may reduce the need to pre-bolus
- Disadvantages: other rapid-acting insulins are available (ie, Apidra, Humalog, Novolog), studies based on non-inferiority trials

## Expected FDA decision date

An FDA decision regarding the approval of FIAsp is expected in October 2016.

- PDUFA: 10/2016

## brodalumab (Siliq)

Manufacturer: Valeant

### Therapeutic use

Brodalumab is in development for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

- Treatment of moderate-to-severe plaque psoriasis

### Clinical profile

Brodalumab is an interleukin-17 (IL-17) receptor antagonist. It targets the IL-17 pathway similar to products such as Cosentyx® (secukinumab) and Taltz® (ixekizumab). However, Cosentyx and Taltz target the IL-17A cytokine. In contrast, brodalumab is a receptor antagonist, thus, it blocks IL-17A, IL-17F, IL17A/F, and possibly IL-17E from binding to the IL-17 receptor site.

In trials, brodalumab improved the signs and symptoms of plaque psoriasis compared to Stelara (ustekinumab). In the AMAGINE-2 trial, 100% improvement from baseline occurred in 44% of patients in the brodalumab arm vs. 22% in the Stelara arm ($p < 0.001$). Similarly, in the AMAGINE-3 trial, 100% improvement from baseline was achieved in 27%–37% of patients on brodalumab vs. 19% for Stelara. Moreover, in both trials, a greater percentage of patients were clear of lesions as measured by the static Physician Global Assessment.

- IL-17 receptor antagonist
- SC formulation
- Superior to Stelara in improving and clearing plaque psoriasis lesions
- Safety concerns: suicide and suicidal ideation, immunogenic and hypersensitivity reactions, neutropenia, and Candida infections

The most significant concern identified in trials was the risk for suicide and suicidal ideation. Two suicides occurred in the brodalumab studies, with one suicide occurring during an open-label extension period and 19 days after the last brodalumab dose in the trial.

Other notable safety concerns for brodalumab include the potential risk for immunogenic and hypersensitivity reactions. In addition, higher rates of neutropenia and mild-to-moderate Candida infections were reported with brodalumab compared to either Stelara or placebo.

Based on its trials, brodalumab is expected to be dosed every 2 weeks by SC injection.

Continued…

## brodalumab (Siliq) (Continued…)

Manufacturer: Valeant

**Competitive environment**

Brodalumab offers a novel MOA and was found to be superior to Stelara in clinical trials.

However, it requires dosing every 2 weeks, in contrast to Cosentyx and Taltz with maintenance doses given every 4 weeks. Brodalumab will likely also face significant competition from biosimilar Enbrel (etanercept) and biosimilar Humira (adalimumab). Furthermore, the early safety signals of suicide and suicidal ideation are a significant disadvantage with brodalumab compared to its competitors.

On July 19, 2016, an FDA advisory panel voted unanimously to approve brodalumab, but the panel also voted 14-4 in favor of implementing measures to mitigate the suicidal risk. Thus, brodalumab may be approved with a boxed warning and possibly a Risk Evaluation and Mitigation Strategy (REMS) program.

An estimated 7.5 million Americans have psoriasis with moderate-to-severe disease affecting approximately 20% of psoriasis patients.

- Advantages: novel MOA, superior to Stelara
- Disadvantages: reported cases of suicide, frequent dosing vs. competitors, pending biosimilars, and related products are available (ie, Cosentyx, Taltz)
- Possible boxed warning and REMS program due to suicide risk

**Expected FDA decision date**

An FDA decision regarding the approval of brodalumab is expected by November 16, 2016.

- PDUFA: 11/16/2016

# telotristat etiprate

Manufacturers: Lexicon/Ipsen

## Therapeutic use

Telotristat etiprate is in development for the treatment of carcinoid syndrome.

Carcinoid syndrome is a disease affecting thousands of cancer patients with advanced or metastatic carcinoid tumors, a type of neuroendocrine tumor. The syndrome is associated with an array of symptoms including debilitating diarrhea, bronchial constriction, abdominal pain, skin flushing and lesions, and rapid heartbeat. Symptoms are associated with elevated serotonin levels.

- Treatment of carcinoid syndrome

## Clinical profile

Telotristat etiprate is a tryptophan hydroxylase inhibitor, which interrupts serotonin synthesis.

In trials, patients who were inadequately managed on a somatostatin analog received either telotristat or placebo. The telotristat arm achieved greater reductions in mean daily bowel movements (BM) over 12 weeks vs. placebo. In addition, more patients achieved a durable response (defined as $\geq$ 30% reduction in daily BM over at least half the days of the study period) vs. placebo (42%–44% vs. 20%, $p \leq 0.020$).

Urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels, a major metabolite of serotonin, also showed declines ($p < 0.001$). However, improvements in flushing episodes and abdominal pain were not different from placebo ($p > 0.05$).

Adverse events reported in trials with telotristat etiprate use included nausea and depression/depressed mood. But overall treatment-emergent adverse events were comparable to placebo.

In trials, telotristat etiprate was given orally three times per day.

- Tryptophan hydroxylase inhibitor
- Oral formulation
- Greater reductions in mean daily BM vs. placebo
- More patients achieved a durable response vs. placebo
- Adverse events: nausea, depression/depressed mood

## Competitive environment

Telotristat etiprate is an oral drug that offers a novel MOA for treating carcinoid syndrome. In addition, there are limited treatment options for treating carcinoid syndrome.

However, telotristat etiprate requires frequent dosing (three times per day) and it is used primarily for symptom management. Thus, it is not a curative agent.

- Advantages: novel MOA, limited treatment options
- Disadvantages: frequent dosing, not curative

## Expected FDA decision date

Telotristat etiprate is considered an orphan drug and was granted fast track status and priority review for carcinoid syndrome by the FDA.

An FDA decision regarding the approval of telotristat etiprate is expected by November 30, 2016.

- Orphan drug
- Fast track status
- Priority review
- PDUFA: 11/30/2016

## ocrelizumab (Ocrevus)

Manufacturer: Genentech

### Therapeutic use

Ocrelizumab is a fully human monoclonal antibody in development for the treatment of both relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS).

In RMS, there are clear episodes of inflammatory activity followed by remission, though residual symptoms may still remain during remission. In contrast to RMS, PPMS is characterized by a steady worsening in the signs and symptoms of MS without distinct relapses or remission.

Characteristic symptoms of multiple sclerosis include numbness or weakness in the limbs, gait difficulties, loss of bowel and bladder control, and cognition difficulties.

- Treatment of RMS
- Treatment of PPMS

### Clinical profile

Ocrelizumab antagonizes CD20, a cell surface antigen present on normal and mature B-cells. Binding of ocrelizumab to CD20 is thought to elicit an immune response against the B-cells.

In RMS trials comparing ocrelizumab to Rebif® (interferon beta-1a), 46%–47% reduction in annualized relapse rates (ARR) were achieved with ocrelizumab vs. Rebif ($p < 0.0001$). Furthermore, gadolinium-enhancing lesions were reduced by 94%–95% in the ocrelizumab arm vs. Rebif.

In the PPMS trial, a 24% reduction in the risk for clinical disability progression was achieved for at least 12 weeks with ocrelizumab vs. placebo (HR = 0.76, $p = 0.0321$). Moreover, there was a 29% reduction in the time to walk 25 feet over 120 weeks ($p = 0.0404$).

The most common adverse events reported in trials with ocrelizumab use were mild-to-moderate infusion-related reactions.

In trials, ocrelizumab was administered by IV infusion as two 300 mg infusions given 2 weeks apart every 24 weeks.

- CD20 antagonist
- IV formulation
- RMS trials: 46%–47% reduction in ARR
- PPMS trial: 24% reduction in risk for clinical disability progression
- Common adverse event: infusion-related reactions

Continued…

## ocrelizumab (Ocrevus) (Continued…)

Manufacturer: Genentech

**Competitive environment**
If approved, ocrelizumab will be the first FDA-approved drug for PPMS, which accounts for an estimated 10% of all MS patients. Furthermore, ocrelizumab was superior to Rebif in RMS trials, and given its dosing regimen (every 6 months), it could become a preferred treatment option for RMS.

However, ocrelizumab is dosed by IV administration and may require in-office treatments. In addition, other RMS treatments are already available, including several oral alternatives.

The projected U.S. sales for ocrelizumab are $1.4 billion by 2020.

- Advantages: could become the first FDA-approved product for PPMS, dosed every 6 months, superior to Rebif
- Disadvantages: IV administration; other RMS treatments are available including oral options
- Projected U.S. sales are $1.4 billion by 2020

**Expected FDA decision date**
Ocrelizumab was granted breakthrough status by the FDA.

An FDA decision regarding the approval of ocrelizumab is expected by December 28, 2016.

- Breakthrough status
- PDUFA: 12/28/2016

# lutetium-177 octreotate (Lutathera)

Manufacturers: Advanced Accelerator Applications/ Fujifilm

**Therapeutic use**
Lutathera is in development for the treatment of adults with gastroenteropancreatic neuroendocrine tumors (GEP-NET), including foregut, midgut, and hindgut tumors.

- Treatment of GEP-NET

**Clinical profile**
Lutathera is a radiolabeled somatostatin analog (SSA).

Interim data in patients that progressed on octreotide LAR therapy showed greater PFS with Lutathera plus octreotide LAR vs. octreotide LAR alone. While the PFS was 8.4 months with octreotide LAR, the median PFS was not reached for the Lutathera arm at the interim analysis point (HR = 0.21, $p < 0.0001$). The objective response rate was also significant ($p< 0.0004$).

In terms of safety, no data are currently available from Lutathera's late stage trial; however, the most common adverse event in early phase trials was fatigue. In addition, there were no grade 3 or 4 adverse events and no fluid-retention related adverse events in the early phase trial.

In trials, Lutathera was given IV at 8 week intervals, but could be extended up to 16 weeks to accommodate for resolving acute toxicity.

- Radiolabeled SSA
- IV formulation
- PFS: not reached with Lutathera vs. 8.4 months with octreotide LAR
- Common adverse event: fatigue

**Competitive environment**
There are limited treatment options for GEP-NET patients who are not adequately managed on SSAs. Thus, Lutathera offers another treatment option for these patients.

In addition, median PFS was not reached by the interim analysis, showing significant benefit over octreotide LAR.

However, Lutathera still requires IV administration. Moreover, its pivotal trial only included patients with midgut carcinoid tumors, so the benefit of Lutathera in other GEP-NET tumors is not clear at this time.

The U.S. prevalence of GEP-NET is approximately 35 per 100,000 persons.

- Advantages: limited treatment options, median PFS not reached by interim analysis point
- Disadvantages: IV administration, study only in midgut carcinoid tumors
- U.S. prevalence ~ 35:100,000

**Expected FDA decision date**
Lutathera is an orphan drug and was granted fast track status by the FDA.

An FDA decision regarding the approval of Lutathera is expected by December 2016.

- Orphan drug
- Fast track status
- PDUFA: 12/2016

## solithromycin (Solithera)

Manufacturers: Cempra/Toyama Chemical/Merck

**Therapeutic use**
Solithromycin is in development for the treatment of community acquired bacterial pneumonia (CABP).

- Treatment of CABP

**Clinical profile**
Solithromycin is a 4th generation macrolide, but unlike existing macrolides, solithromycin targets three sites on bacterial ribosomes, which increases its activity against resistant strains. It also exhibits broader spectrum bacterial activity.

In trials, solithromycin was non-inferior to Avelox® (moxifloxacin), a common fluoroquinolone used in CABP.

The most common adverse events reported in trials with solithromycin use were headache, diarrhea, nausea, emesis, and dizziness. There were more frequent treatment-emergent adverse events with solithromycin vs. Avelox; however, this was primarily due to infusion-related reactions, including injection site pain.

Solithromycin did not exhibit concerns with QT prolongation.

In trials, solithromycin was administered IV or orally once daily for 5–7 days.

- 4th generation macrolide
- Oral and IV formulations
- Non-inferior to Avelox
- Common adverse events: headache, diarrhea, nausea, emesis, and dizziness
- No known risk of QT prolongation

**Competitive environment**
Solithromycin is an oral and IV administered antibacterial agent with broad-spectrum coverage and no known resistance.

However, the trials only demonstrated non-inferiority to Avelox.

Generic antibiotics are also available, including various fluoroquinolones, beta-lactams, and vancomycin.

- Advantages: available as oral and IV formulations, broad-spectrum coverage, no known resistance
- Disadvantage: generic antibacterial alternatives are available

**Expected FDA decision date**
Solithromycin is a Qualified Infectious Disease Product (QIDP) and was granted fast track status by the FDA. QIDP is a special designation for antibacterial and antifungal agents intended to treat serious or life-threatening infections. It increases the potential for an expedited review by the FDA and permits an additional 5 years of market exclusivity on top of other allowable exclusivities.

An FDA decision regarding the approval of solithromycin is expected by December 2016.

- QIDP status
- Fast track status
- PDUFA: 12/2016

# oxymetazoline

Manufacturer: Allergan

**Therapeutic use**
Oxymetazoline is in development for the treatment of persistent facial erythema associated with rosacea in adults.

- Treatment of persistent facial erythema associated with rosacea

**Clinical profile**
Oxymetazoline is an alpha adrenergic receptor agonist. Topical application is thought to reduce blood flow to the face, thereby, reducing redness.

Oxymetazoline is currently in phase 3 trials; however, data are not available yet.

A long-term, single-arm safety and efficacy trial is also ongoing.

- Alpha adrenergic receptor agonist
- Topical formulation

**Competitive environment**
Oxymetazoline is another treatment alternative for patients with rosacea.

At this time, there are no phase 3 data available regarding its safety or efficacy. However, oxymetazoline is for the symptomatic management of facial redness and does not target the underlying disease state of rosacea.

Other treatment options are available, including topical alpha adrenergic agonists, such as Mirvaso® (brimonidine). Mirvaso is selective for alpha-2 receptors.

The projected U.S. sales for oxymetazoline are $60 million by 2020.

- Advantage: another treatment option for patients
- Disadvantages: no safety or efficacy data, does not target underlying disease, similar product is available (ie, Mirvaso)
- Projected U.S. sales are $60 million by 2020

**Expected FDA decision date**
An FDA decision regarding the approval of oxymetazoline is expected between November 2016 and January 2017.

- PDUFA: 11/2016–1/2017

## 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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