<table>
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<tr>
<th>PIPELINE DRUG</th>
<th>CURRENT STATUS</th>
<th>ANTICIPATED APPROVAL</th>
<th>WHAT IS THIS DRUG BEING DEVELOPED FOR?</th>
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<tr>
<td>allopurinol / lesinurad</td>
<td>NDA Filed</td>
<td>2017 10/4/2017</td>
<td>Fixed dose combination of Zurampic® (lesinurad) and allopurinol for the treatment of gout; oral (PO).</td>
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<tr>
<td>Duzallo - Ironwood</td>
<td></td>
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<tr>
<td>amantadine ER</td>
<td>NDA Filed</td>
<td>2017 08/24/2017</td>
<td>An oral, extended-release (ER) formulation of amantadine for improving levodopa-induced dyskinesia in patients with Parkinson’s disease (PD); PO.</td>
</tr>
<tr>
<td>ADS-5102 - Adamis</td>
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<tr>
<td>amphetamine salts, triple-bead</td>
<td>NDA Filed</td>
<td>2017 06/20/2017</td>
<td>Triple-bead mixed amphetamine salt as a treatment for attention-deficit/hyperactivity disorder (ADHD) in adults; PO.</td>
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<tr>
<td>mix SHP465 - Shire</td>
<td></td>
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<tr>
<td>amphetamine XR, oral suspension</td>
<td>NDA Filed</td>
<td>2017 09/15/2017</td>
<td>NT-0201 is a once-daily extended-release liquid formulation of amphetamine for treatment for ADHD; PO.</td>
</tr>
<tr>
<td>NT-0201 - Neos</td>
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<tr>
<td>andexanet alfa AndexXa - Portola/Bayer</td>
<td>Complete Response Priority Review</td>
<td>2017</td>
<td>Andexanet alfa is being developed for use as a Factor Xa (FXa) inhibitor reversal agent. It works by binding to FXa inhibitors, preventing them from inhibiting FXa and allowing for normal hemostasis; intravenous (IV). Breakthrough Therapy</td>
</tr>
<tr>
<td>betrixaban Portola</td>
<td>NDA Filed</td>
<td>2017 06/24/2017 Priority Review</td>
<td>Factor Xa inhibitor anticoagulant for extended-duration prophylaxis of venous thromboembolism (VTE) in acute medically ill patients with risk factors for VTE; PO.</td>
</tr>
<tr>
<td>brimonidine 0.025% (OTC)</td>
<td>NDA Filed</td>
<td>2017 12/27/2017</td>
<td>Topical vasoconstrictor (brimonidine) formulation to be used over-the-counter (OTC) as an eye drop to relieve redness of the eye due to minor eye irritations; ophthalmic solution.</td>
</tr>
<tr>
<td>Luminesse™ - Bausch &amp; Lomb</td>
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<tr>
<td>delafloxacin Baxdela - Melinta</td>
<td>NDA Filed</td>
<td>2017 06/19/2017</td>
<td>Delafloxacin is a novel fluoroquinolone for the treatment of skin and soft tissue infections FDA has designated delafloxacin as a Qualified Infectious Disease Product (QIDP); PO and IV.</td>
</tr>
<tr>
<td>dihydroergotamine Semprana - Allergan</td>
<td>NDA Filed</td>
<td>2018</td>
<td>An inhaled formulation of dihydroergotamine (DHE) the treatment of acute migraine headaches; inhalation therapy.</td>
</tr>
<tr>
<td>epinephrine pre-filled syringe</td>
<td>NDA Filed</td>
<td>2017 06/16/2017</td>
<td>Pre-filled single-dose syringe formulation of adrenaline for emergency treatment of Type I allergic reactions including anaphylaxis; subcutaneous (SQ).</td>
</tr>
<tr>
<td>Adamis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>erenumab AMG334 - Amgen/Novartis</td>
<td>Phase 3</td>
<td>2018</td>
<td>AMG 334 is a calcitonin gene-related peptide (CGRP) receptor antagonist monoclonal antibody for the treatment and prevention of chronic migraine; monthly SQ.</td>
</tr>
</tbody>
</table>
## Pipeline Report

### Brand Drugs

**July 2017**

<table>
<thead>
<tr>
<th>Pipeline Drug</th>
<th>Current Status</th>
<th>Anticipated Approval</th>
<th>What Is This Drug Being Developed For?</th>
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<tbody>
<tr>
<td>ertugliflozin Merck/Pfizer</td>
<td>NDA Filed</td>
<td>2017 Dec. 2017</td>
<td>A sodium glucose cotransporter 2 (SGLT2) inhibitor for treating Type 2 diabetes. Blocking this receptor results in excretion of excess glucose in the urine, decreasing blood glucose levels; PO.</td>
</tr>
<tr>
<td>glycopyrrolate nebulization solution SUN101 - Sunovion</td>
<td>NDA Filed</td>
<td>2017 5/29/2017</td>
<td>Glycopyrolate, a long-acting muscarinic antagonist, for treating chronic obstructive pulmonary disorder (COPD); nebulization solution.</td>
</tr>
<tr>
<td>insulin glargine MK-1293 - Merck / Samsung Bioepis</td>
<td>NDA Filed</td>
<td>2017 2Q 2017</td>
<td>Follow-on insulin glargine product. It will be a brand competitor to Lantus (not a biosimilar); SQ.</td>
</tr>
<tr>
<td>methylphenidate XR-ODT Cotempla XR-ODT - Neos</td>
<td>NDA Filed</td>
<td>2017 6/19/2017</td>
<td>Extended-release formulation of methylphenidate delivered in an orally disintegrating tablet for treating ADHD; PO.</td>
</tr>
<tr>
<td>morphine sulfate ER Arymo ER - Egalet</td>
<td>NDA Filed</td>
<td>2017</td>
<td>Abuse-deterrent formulation of morphine sulfate ER. This product will be available in similar dosage strengths as MS Contin (morphine sulfate); PO.</td>
</tr>
<tr>
<td>ozenoxacin Ferrer</td>
<td>NDA Filed</td>
<td>2017 06/27/2017</td>
<td>Ozenoxacin belongs to a new generation of non-fluorinated quinolones for the topical treatment of impetigo in patients aged 2 months and older; topical cream.</td>
</tr>
<tr>
<td>semaglutide Novo Nordisk</td>
<td>NDA Filed</td>
<td>2017 12/5/2017</td>
<td>Once weekly GLP-1 analog for treating type 2 diabetes; SQ.</td>
</tr>
<tr>
<td>umecclidinium/vilanterol/fluticasone furoate Closed Triple Combination – GSK / Theravance</td>
<td>NDA Filed</td>
<td>2017 09/21/2017</td>
<td>Umeclidinium / vilanterol / fluticasone furoate triple combination brings together two bronchodilators the long acting muscarinic antagonist (umeclidinium) and the long acting beta agonist (vilanterol) with the corticosteroid fluticasone furoate.</td>
</tr>
<tr>
<td>varicella zoster vaccine Shingrix - GlaxoSmithKline</td>
<td>BLA Filed</td>
<td>2017 10/24/2017</td>
<td>Recombinant shingles (varicella zoster virus) vaccine for the prevention of herpes zoster in people aged 50 years and older; intramuscularly (IM).</td>
</tr>
</tbody>
</table>
allopurinol / lesinurad (Duzallo - Ironwood)

**Current Status:** This product is currently under FDA review with an action date of October 4, 2017.

**Route of Administration/Dosing:** Oral (PO) therapy.

**Proposed Indication(s):** Fixed-dose combination of Zurampic® (lesinurad) and allopurinol for once-daily oral treatment of hyperuricemia in patients with uncontrolled gout.

**Mechanism of Action:** Lesinurad is a URAT-1 inhibitor. Allopurinol is a generically-available xanthine oxidase inhibitor (XOI).

**Patient Impact:** It is estimated that roughly half of the four million gout patients in the U.S. treated with a XOI, either allopurinol or febuxostat, are uncontrolled and are not achieving target serum uric acid (sUA) levels <6 mg/dL as recommended by the American College of Rheumatology (ACR).

**Comments:** Gout is a highly symptomatic and painful form of inflammatory arthritis affecting more than nine million people in the U.S. It is caused by an underlying metabolic disorder, hyperuricemia – high levels of uric acid in the blood – and can lead to painful flares, characterized by excruciating pain, inflammation, swelling and tenderness in one or more joints. Gout is not only a lifestyle disease, but has a hereditary component. While diet and lifestyle changes are important in managing gout and its comorbidities, they are often not enough to get patient sUA levels to target. More than four million patients are treated with a XOI for gout in the U.S. Of these, an estimated two million patients are uncontrolled and are not achieving target sUA levels <6 mg/dL as recommended by the ACR, despite treatment with an XOI alone. These patients continue to suffer from flares, and may face serious long-term consequences that can result from having uncontrolled sUA levels. ACR guidelines recommend adding a uricosuric agent, like Zurampic, to a XOI in patients who are not achieving target sUA levels. Duzallo is a fixed dose combination therapy of Zurampic and allopurinol for use in these patients.

amantadine ER (ADS-5102 - Adamis)

**Current Status:** This product is currently under FDA review with an action date of Aug. 24, 2017.

**Route of Administration/Dosing:** PO therapy (once daily at bedtime).

**Proposed Indication(s):** Adjunctive therapy for treatment of levodopa-induced dyskinesia (LID) in patients with Parkinson’s disease (PD).

**Mechanism of Action:** The mechanism of action of amantadine in the treatment of PD is not known. However, it is thought that the drug may have direct and indirect effects on dopamine neurons.

**Patient Impact:** Parkinson’s disease is a progressive, incurable neurological disorder associated with a loss of dopamine generating cells in the brain that results in a complex array of symptoms. It is primarily associated with progressive loss of motor control, but there are many more non-motor symptoms. Parkinson’s disease impacts an estimated one million people in the U.S. Moderate-to-severe LID affects up to 25% of treated PD patients. In the U.S., approximately 150,000 to 200,000 people with Parkinson’s suffer from LID.

**Comments:** ADS-5102 is an extended-release (ER) formulation of amantadine. The current formulation of amantadine is usually administered twice daily. Therefore, an ER formulation may provide a dosing convenience for patients requiring amantadine as adjunctive therapy. ADS-5102 is under investigation for treatment of LID. It is estimated that up to 25% of treated PD patients have moderate-to-severe LID. Currently, there are no approved drug therapies for this condition. Clinicians either restrict levodopa dosing or try off-label alternatives. The only approved treatment for LID is deep brain stimulation, which requires surgery and is not a viable option for most patients. This product is currently under FDA review with a PDUFA date of 08/24/2017.
amphetamine salts, trible-bead mix (SHP465 - Shire)

**Current Status:** This product is currently under FDA review with an action date of June 20, 2017.

**Route of Administration/Dosing:** PO therapy.

**Proposed Indication(s):** Once-daily treatment for attention-deficit/hyperactivity disorder (ADHD).

**Mechanism of Action:** SHP-465 is a mixed salt of single entity amphetamine (three-component) which is formulated as a capsule to extend the release of drug. It targets dopamine transporter and noradrenaline transporter.

**Patient Impact:** It is estimated that between 3-5% of children have ADHD, or approximately 2 million children in the United States. ADHD is one of the most common childhood disorders and can continue through adolescence and into adulthood.

**Comments:** ADHD is a neurodevelopmental disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development and is inconsistent with developmental level. An estimated 4.4% of adults have ADHD in the U.S. When applied to the full U.S. adult population aged ≥18, approximately 10.5 million adults are estimated to have ADHD. SHP465, a long-acting, triple-bead, mixed amphetamine salt formulation, is a potential once-daily treatment for ADHD. The FDA is expected to provide a decision around June 20, 2017 with launch plans for the second half of 2017. Shire first submitted the New Drug Application (NDA) in 2006, but was granted an "approvable" status. FDA requested additional data for use in children. Exclusivity for this product would help extend to 2029.

amphetamine XR, oral suspension (NT-0201 - Neos)

**Current Status:** This product is currently under FDA review with an action date of September 17, 2017.

**Route of Administration/Dosing:** ER, once-daily, PO suspension.

**Proposed Indication(s):** Treatment of ADHD.

**Mechanism of Action:** This product is an amphetamine formulation for treating ADHD. Amphetamines are sympathomimetic agents. It acts by stimulating the release of norepinephrine from central adrenergic receptors. It also induces the release of dopamine from the mesocorticolimbic system and the nigrostriatal dopamine systems.

**Patient Impact:** It is estimated that between 3-5% of children have ADHD, or approximately 2 million children in the U.S.

**Comments:** Extended-release oral liquid suspension formulation of the stimulant for treatment of ADHD. The company is developing patient-friendly treatment options of the stimulant medications that are most widely prescribed for the treatment of ADHD. NT-0201 contains amphetamine loaded onto a mixture of immediate-release and polymer-coated delayed-release resin particles, and using the company's patented dynamic time release suspension, or DTRS, technology, Neos is able to create an amphetamine XR liquid suspension. NT-0201 is designed to be shelf stable for 24 months, without requiring refrigeration or reconstitution. If approved, the company plans to sell it by the end of 2017 alongside Adzenys XR-ODT™.

andexanet alfa (AndexXa - Portola/Bayer)

**Current Status:** Complete Responses Letter (CRL) issued. Portola expects to resubmit the BLA in 2017.

**Route of Administration/Dosing:** Intravenous (IV) therapy.

**Proposed Indication(s):** Universal Factor Xa (FXa) inhibitor antidote, to reverse the activity of FXa inhibitors and low-molecular weight heparin (LMWH) in patients experiencing a major bleeding event or require emergency surgery.

**Mechanism of Action:** Andexanet alfa is a recombinant protein that is structurally distinct from native FXa, and acts as a decoy for FXa inhibitors in the blood; this prevents them from inhibiting the activity of native FXa, thereby allowing native FXa to participate in restoring hemostasis.
**Patient Impact:** One of the major drawbacks to the new oral anticoagulants (FXa Inhibitors) is that no reversal agents are currently available. To alleviate bleeding due to these anticoagulants, providers have used prothrombin complex concentrates, recombinant factor VIIa, and/or fresh frozen plasma. Annually, around 1-4% of patients treated with FXa inhibitors may experience major bleeding and 1% may require emergency surgery.

**Current Therapies:** No direct acting reversal agents available. Platelet transfusion required for rapid reversal. Praxbind® (idarucizumab) approved on 10/16/2015 (Pradaxa® only).

**Pipeline Product(s):** aripazine (PER977 - Perosphere): Phase II/III (2018).

**Comments:** Potential first-in-class recombinant, modified FXa molecule that is being developed as an antidote for patients receiving a FXa inhibitor who suffer a major bleeding episode or who may require emergency surgery. As there are no specific reversal agents for FXa inhibitors yet, andexanet alfa potentially addresses an unmet need. It is being developed as a "companion" product to betrixaban, Portola's once-daily, oral FXa inhibitor. The product is designed to induce clotting for either the treatment of acute bleeding, or to prevent such bleeding in those undergoing surgery who are currently on FXa inhibitors or LMWH for other medical conditions. Andexanet alfa is a recombinant protein that is structurally distinct from native FXa, and acts as a decoy for FXa inhibitors in the blood; this prevents them from inhibiting the activity of native FXa, thereby allowing native FXa to participate in restoring hemostasis. The drug does not seem to be effective against the factor IIa inhibitor dabigatran. 09/16/2015 - Results from ANNEXA-R study (Phase III) demonstrated that andexanet alfa rapidly and significantly reversed the anticoagulant effect of rivaroxaban as measured by anti-FXa activity (>90% reduction of mean anti-FXa activity within five minutes of the end of administration) compared with placebo (p<0.0001). 11/11/2015: Portola released positive data from the second part of andexanet’s Phase III ANNEXA-R trial. The study demonstrated that administration of an IV bolus of andexanet alfa followed by a continuous two-hour infusion produced rapid reversal of the anticoagulant effect of rivaroxaban and sustained it for the duration of the infusion. Aug. 18, 2016 update: FDA issued a ‘complete response’, requesting additional information prior to granting approval. The agency wants additional information related to the drugs manufacturing and for the inclusion of Savaysa® and Lovenox® in the prescribing information. Dec. 19, 2016 - Portola enters into $50 Million Loan Agreement with Bristol-Myers Squibb and Pfizer for continued development of andexanet alfa. Portola expects to resubmit the BLA in 2017.

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**betrixaban (Portola)**

**Current Status:** This product is currently under FDA review with an action date of October 25, 2017.

**Route of Administration/Dosing:** Once daily PO therapy.

**Proposed Indication(s):** Prophylaxis of venous thromboembolism (VTE) in acute medically ill patients with risk factors for VTE.

**Mechanism of Action:** An oral direct FXa inhibitor.

**Patient Impact:** An estimated 22.5 million acute medically ill patients in the U.S, Canada, France, Germany, Italy, Japan, and the United Kingdom are at risk of developing VTE, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), either while in the hospital or following discharge. Each year, more than 1 million VTE events and 150,000 VTE-related deaths occur in acute medically ill patients in these countries, despite the standard use of injectable enoxaparin and other heparins. More than half of VTE events occur after the patient is discharged from the hospital. However, no anticoagulant, including enoxaparin or any of the marketed oral FXa inhibitors, is approved for extended VTE prophylaxis for acute medically ill patients who are hospitalized.

**Current Therapies:** Coumadin® (warfarin - BMS), Eliquis® (apixaban - BMS/Pfizer), Pradaxa® (dabigatran - BI), and Xarelto® (rivaroxaban - Janssen).

**Comments:** Portola has submitted a NDA seeking approval to market betrixaban for extended-duration prophylaxis of VTE in acute medically ill patients with risk factors for VTE. Betrixaban, an FDA fast track-designated investigational drug, is an oral, once-daily FXa inhibitor anticoagulant. It directly inhibits the activity of FXa, to prevent life-threatening thrombosis. Betrixaban has distinct properties that may allow it to demonstrate clinical benefit without the significant imbalance in the risk of fatal bleeding seen with other agents in the class: it has a 19-25 hour half-life for once-daily
dosing: a low peak-to-trough drug concentration ratio that minimizes anticoagulant variability; low renal clearance; and no significant CYP3A4 metabolism, which may reduce the risk of drug-drug interactions.

brimonidine 0.025% (OTC) (Luminesse™ - Bausch & Lomb)

Current Status: This product is currently under FDA review with an action date of December 27, 2017.

Route of Administration/Dosing: Ophthalmic therapy.

Proposed Indication(s): Over-the-counter (OTC) treatment of ocular redness.

Mechanism of Action: Brimonidine is an alpha adrenergic receptor agonist.

Patient Impact: According to the manufacturer, more than 14 million households use OTC eye drops to treat ocular redness. Luminesse will compete with the other agents for a portion of market share.

Comments: Bausch + Lomb announced that the FDA has accepted the NDA for brimonidine tartrate ophthalmic solution, 0.025%, and set a PDUFA action date of December 27, 2017. Brimonidine is a topical vasoconstrictor formulation to be used OTC as an eye drop to relieve redness of the eye due to minor eye irritations. If approved, this will be the first OTC product developed with brimonidine tartrate for the treatment of ocular redness. Six clinical studies were conducted to evaluate the safety and effectiveness of low-dose brimonidine in relieving ocular redness, including a study to demonstrate the absence of IOP-lowering potential of low-dose brimonidine. Bausch + Lomb also conducted a comprehensive review of all post-marketing safety data, as the active ingredient brimonidine tartrate is typically found to be used in prescription ophthalmic products. The drug was found to be highly efficacious and safe with low risk of tachyphylaxis and rebound congestion, which are both common to currently available OTC redness reliever eye drops.

delaflloxacin (Baxdela - Melinta)

Current Status: This product is currently under FDA review with an action date of 06/19/2017.

Route of Administration/Dosing: PO and IV therapies.

Proposed Indication(s): Treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by gram-positive (methicillin-resistant Staphylococcus aureus, or MRSA) and gram-negative bacteria.

Mechanism of Action: Delaflloxacin inhibits the bacterial DNA gyrase enzyme which is necessary for DNA replication.

Patient Impact: The company estimates that nearly 3 million patients are hospitalized annually in the U.S. with serious skin infections. It also estimates that quinolones are used for treating one out of three hospital-treated infections. However, Baxdela will compete with generically-available quinolones (and other antibacterial products) for treating many of these infections. Its extended spectrum may result in the product being reserved for bacterial infections that are resistant to other therapies.

Comments: Baxdela is an experimental drug candidate currently in clinical development belonging to the well-established quinolone class of antibiotics, which are currently used in one out of three hospital-treated infections. It has enhanced antimicrobial activity, including activity against MRSA, a major cause of serious skin infections, a favorable tolerability profile, and convenient administration with both IV and PO forms. Melinta Therapeutics’ delaflloxacin is currently being assessed in two Phase III studies within the PROCEED program for the treatment of ABSSSI caused by gram-positive (MRSA) and gram-negative bacteria, an indication for which the U.S. FDA has designated delaflloxacin a Qualified Infectious Disease Product (QIDP). The company is also conducting the Phase III PROCEEDing clinical study of a single, oral dose of delaflloxacin (900 mg) for the treatment of uncomplicated gonorrhea. The FDA also designated delaflloxacin a QIDP for this indication. Baxdela will compete with generically-available quinolones for treating many of these skin infections. It has been designated QIDP by the FDA, which provides for priority (8 month) review.
**dihydroergotamine (Semprana - Allergan)**

**Current Status:** A second CRL issued in June 2014 related to the manufacturing process. Company expects to resubmit application by end of 2016.

**Route of Administration/Dosing:** Inhalation (asthma inhaler-like device).

**Proposed Indication(s):** Treatment for acute migraine.

**Mechanism of Action:** The activity of dihydroergotamine (DHE) in migraines is generally attributed to the agonist effect at 5-HT1D receptors.

**Patient Impact:** Migraine affects 10-20% of the world population and is listed in the top four neurologic disabling conditions by the World Health Organization. Up to 1/3 of patients do not adequately respond to therapy with a triptan. Triptans have also been shown to be more effective when taken earlier in the headache phase of a migraine attack. Semprana is an inhaled formulation of DHE intended to offer a fast onset of action, similar to an IV infusion, but without the need for an injection. DHE is effective in both early and late phases of a migraine attack. This formulation would allow patients to administer DHE at home.

**Current Therapies:** Oral, injectable and intranasal “triptans”, injectable DHE, intranasal DHE (Migranal® – Valeant).

**Comments:** Semprana (formerly known as Levadex) is an inhaled formulation of the ergot alkaloid, DHE, for treating migraine headaches. It is intended to offer a fast onset of action, similar to an IV infusion, but without the need for an injection. The inhaled formulation may also have fewer side effects (e.g. nausea) compared to the injectable formulation. DHE has been shown to be effective in both early and late phases of migraine headaches, whereas triptans are generally most effective for treating the early phases. 08/24/2016: NDA refiling for migraine in early 2017 (Cowen and Company).

**epinephrine pre-filled syringe (Adamis)**

**Current Status:** This product is currently under FDA review with an action date of 07/07/2017.

**Route of Administration/Dosing:** Subcutaneous (SQ) therapy.

**Proposed Indication(s):** Pre-filled single-dose syringe of adrenaline for emergency treatment of Type I allergic reactions including anaphylaxis.

**Mechanism of Action:** Epinephrine is a direct-acting sympathomimetic drug that acts as an agonist at alpha and beta-adrenergic receptors. It also causes vasoconstriction, counteracting the vasodilation, and resulting hypotension, associated with anaphylaxis.

**Patient Impact:** It is estimated that up to 8% of U.S. children under the age of 18 have a food allergy, and approximately 38% of those with a food allergy have a history of severe reactions.

**Current Therapies:** EpiPen® (epinephrine - Mylan); Auvi-Q® (epinephrine - Sanofi) - Removed from the market (recall).

**Pipeline Product(s):** Generic Epipen® (Teva): 2H:2016 (pending FDA approval)

**Comments:** Pre-filled single-dose syringe of adrenaline for emergency treatment of Type I allergic reactions including anaphylaxis. Adamas resubmitted the NDA in December 2015. The previous submission was given a “complete response” letter by FDA in March 2015. The agency had questions relating to the volume of dose delivered by the syringe, including the ability to deliver volume within the levels contained in the labeling claim and as required by the FDA. The epinephrine pre-filled syringe is back under FDA review with an estimated PDUFA date of June 7, 2016. Once approved, this product will compete with EpiPen, a product that had approximately $885 in annual sales (2014), for market share. Generics to EpiPen were originally anticipated during the second half of 2015. However, Teva received a CRL for its proposed generic, delaying it until 2017.
erenumab (AMG334 - Amgen/Novartis)

**Current Status:** Phase III. Regulatory submission is planned for early 2017. Given a standard review, this product could be approved in early 2018.

**Route of Administration/Dosing:** SQ therapy (once monthly).

**Proposed Indication(s):** Treatment of episodic and chronic migraine.

**Mechanism of Action:** Erenumab is a fully human monoclonal antibody under investigation for the prevention of migraine. Erenumab specifically targets the calcitonin-gene-related-peptide (CGRP) receptor, which is believed to transmit signals that can cause incapacitating pain.

**Patient Impact:** Impact approximately 12% of the U.S. population – approximately 18% of women and 6% of men.

**Current Therapies:** Oral, injectable and intranasal “triptans”, injectable dihydroergotamine, intranasal dihydroergotamine (Migranal® – Valeant).

**Comments:** Erenumab is a novel migraine treatment that targets the CGRP pathway. Migraines are currently thought to begin with dilation of cranial blood vessels, which activates perivascular trigeminal sensory nerve fibers. These in turn release the neuropeptide CGRP, which contributes to vasodilation, neurogenic inflammation, and subsequently the transmission of pain impulses. Amgen’s erenumab (developed with Novartis, NVS, [MP]) targets the CGRP receptor whereas Alder’s ALD403, Teva’s TEV-48125, and Eli Lilly’s (LLY, [OP]) galcanezumab bind CGRP itself (the ligand). All four compounds have initiated Phase III development in what is becoming an increasingly crowded market. Amgen’s product is leading the way and is expected to reach the market in early 2018.

ertugliflozin (Merck / Pfizer)

**Current Status:** Phase III clinical trials. Once submitted, a 12 month review is anticipated.

**Route of Administration/Dosing:** Once daily PO therapy.

**Proposed Indication(s):** For use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

**Mechanism of Action:** Ertugliflozin is an inhibitor of subtype 2 sodium-glucose transport protein (SGLT2), which is responsible for at least 90% of the glucose reabsorption in the kidney (SGLT1 being responsible for the remaining 10%).

**Patient Impact:** Approximately 25.8 million Americans have type 1 or type 2 diabetes. Spending on diabetes medications totaled $22 billion in 2012, according to IMS Health. Type 2 diabetes (T2D) is the most common type, accounting for an estimated 90% of all diabetes cases. Diabetes is a chronic disease that occurs when the body either does not properly produce, or use, the hormone insulin. Diabetes was estimated to cost the U.S. $245 billion in direct medical costs and reduced productivity in 2012.

**Current Therapies:** Invokana® (canagliflozin - Janssen), Farxiga® (dapagliflozin - AZ) and Jardiance® (empagliflozin - Lilly).

**Pipeline Product(s):** Bexagliflozin (Chugai) - SGLT-2 inhibitor - Phase III; sotagliflozin (Lexicon) - SGLT-1 and SGLT-2 inhibitor – Phase II.

**Comments:** Ertugliflozin is a SGLT-2 inhibitor that comes in a once-daily pill. Originally, Pfizer was developing and testing ertugliflozin as a drug to be taken alone. However, this partnership will allow the companies to also develop ertugliflozin combination pills: ertugliflozin plus Merck’s DPP-4 inhibitor Januvia® (sitagliptin) and ertugliflozin plus Januvia and metformin. These combinations should make taking medication much easier, since they will reduce the number of pills from two or three to one. 03/04/2016 - During its earning call, the company indicated plans to file ertugliflozin (alone) and two fixed-dose combination tablets (ertugliflozin+sitagliptin; ertugliflozin+metformin) by the end of 2016.
**glycopyrrolate nebulization solution (SUN101 - Sunovion)**

**Current Status:** This product is currently under FDA review with an action date of May 29, 2017.

**Route of Administration/Dosing:** Inhalation via the company's proprietary eFlow Nebulizer system (twice daily).

**Proposed Indication(s):** Treatment of patients with moderate-to-very-severe chronic obstructive pulmonary disease (COPD).

**Mechanism of Action:** Long-acting muscarinic antagonist (LAMA).

**Patient Impact:** This product will compete with the LAMA inhalers. Thirty million patients in the U.S. suffer from COPD, also known as emphysema and chronic bronchitis. An estimated 6 million patients are receiving treatment. COPD is the fourth leading cause of death in the U.S.

**Comments:** Nebulizer formulation of the LAMA for delivery via Sunovion's investigational eFlow electronic closed nebulizer system for long-term maintenance treatment of adults with moderate-to-very-severe COPD. This product combines a nebulized drug and device and is designed to deliver the medication in two to three minutes compared to a standard jet nebulizer that typically takes up to 10 minutes. If approved, SUN-101/eFlow would be the first nebulized LAMA for patients with COPD.

**insulin glargine (MK-1293 - Merck / Samsung Bioepis)**

**Current Status:** This product is currently under FDA review with an action date in the second quarter of 2017.

**Route of Administration/Dosing:** SQ therapy.

**Proposed Indication(s):** Injectable treatment for diabetes.

**Mechanism of Action:** MK-1293 is a form of insulin glargine for use as an injection. Insulin glargine is a recombinant human insulin analog that is a long-acting blood-glucose lowering agent. Insulin and its analogs lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. MK-1293 is expected to have a flatter and more prolonged profile than Lantus®.

**Patient Impact:** If approved MK-1293 would provide patients with another form of once daily insulin analog. An estimated 22.5 million adults will be diagnosed with T2D by 2014. In the US, basal insulin market is estimated at more than $6 billion.

**Comments:** MK-1293 is a new insulin glargine with the same amino acid sequence as Lantus. The estimated PDUFA date for this product is in the second quarter of 2017. The insulin copies are considered follow-on biologics rather than biosimilars in the U.S. because Lantus, though a complex drug, was approved under an NDA, not a BLA. Merck is, therefore relying on the 505(b)(2) pathway rather than the 351(k) pathway for biosimilars to secure regulatory approval in the U.S., while in Europe the drugs are considered biosimilars. At the American Diabetes Association (ADA), Merck said that both of the Phase III studies achieved their primary endpoint, showing the non-inferiority of MK-1293 to Lantus in change from baseline A1c after 24 weeks. The studies met secondary endpoints too of statistical A1c equivalence to Lantus, and safety was also similar to the safety of Lantus.

**methylphenidate XR-ODT (Cotempla XR-ODT - Neos)**

**Current Status:** This product is currently under FDA review with an action date of June 20, 2017.

**Route of Administration/Dosing:** PO therapy (daily).

**Proposed Indication(s):** Extended-release formulation of the methylphenidate delivered in an orally disintegrating tablet (ODT) for treatment of ADHD.

**Mechanism of Action:** ADHD and other similar conditions are believed to be linked to sub-performance of the dopamine and norepinephrine functions in the brain, primarily in the prefrontal cortex, responsible for executive function (e.g., reasoning, inhibiting behaviors, organizing, problem solving, planning, etc.). Methylphenidate's mechanism of action involves the inhibition of catecholamine reuptake, primarily as a dopamine reuptake inhibitor.
**Patient Impact:** According to the CDC, ADHD is one of the most common childhood disorders and can continue through adolescence and adulthood. It is estimated to affect 5% of children and 2.5% of adults in the U.S.

**Comments:** Neos therapeutics is developing Cotempla XR-ODT (methylphenidate XR-ODT) as a once-daily treatment of ADHD. The product uses a proprietary modified-release drug delivery and ODT technology platform to deliver methylphenidate ER as an ODT, for the treatment of ADHD. ADHD is a condition characterized by inattention, hyperactivity, impulsiveness, or a combination. In November 2015, Neos received a FDA-issued CRL for Cotempla XR-ODT requiring that the company conduct a bridging study to demonstrate bioequivalence between the clinical trial material and the to-be-marketed drug product, including an assessment of food effect, and to provide validation and three months of stability data. This resubmission follows the successful completion of the bioequivalence bridging study, and the validation and stability campaigns. The PDUFA date is June 20, 2017. Neos Therapeutics recently received approval and launched Adzenys XR-ODT™ (amphetamine).

**Current Status:** This product is currently under FDA review with an action date of October 14, 2016. Date has passed.

**Route of Administration/Dosing:** Twice daily PO therapy.

**Proposed Indication(s):** Management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatments are inadequate.

**Mechanism of Action:** Abuse-deterrent opioid product containing the opioid analgesic, morphine.

**Patient Impact:** Arymo ER is another long-acting opioid agonist for treating severe pain. It will compete with available long-acting brand and generic opioid products.

**Pipeline Products:** The following long-acting opioid formulations are currently under FDA review: hydrocodone ER (Vantrela™ - Teva); oxycodone / naltrexone ER (Troxyca® ER - Pfizer); oxycodone, ER (Remoxy® – Pain Therapeutics)

**Comments:** Eagle pharmaceuticals has submitted a NDA for Arymo ER, an abuse-deterrent, ER formulation of morphine sulfate. The company has also submitted data demonstrating bioequivalence of Arymo ER 15, 30 and 60mg to equivalent doses of MS Contin (morphine sulfate controlled-release). Arymo ER is seeking labeling claims to deter abuse via IV injection, snorting and oral abuse (crush resistant). Looking forward, as abuse deterrent products become available, legislation and/or FDA may require the use of the abuse deterrent products and/or the removal of the non-abuse deterrent formulations from the market (e.g. Oxycontin - original formulation) in an attempt to help curb the opioid abuse epidemic. Recently, FDA announced a plan will focus on policies that can help reverse the epidemic while continuing to allow patients who are in pain to access effective care. One of the agency's initiatives is to expand access to, and encourage development of, abuse-deterrent formulations of opioid products.

03/01/2016 update: The NDA was accepted by FDA with a PDUFA date of October 14, 2016.

**Current Status:** This product is currently under FDA review with an action date of June 27, 2017.

**Route of Administration/Dosing:** Topical therapy (twice daily).

**Proposed Indication(s):** Topical treatment of impetigo in adults and pediatric patients aged 2 months and older.

**Mechanism of Action:** Non-fluorinated quinolone antibiotic in a 1% cream formulation.

**Patient Impact:** Impetigo is a highly contagious bacterial skin infection. It affects most commonly infants, young children and those involved in close contact sports or living in enclosed environments; it is not common in adults. In the U.S., impetigo is estimated to account for ~10% of the skin problems observed in pediatric clinics. It is also considered the most common bacterial skin infection and third most common skin condition of children.
Current Therapies: Antibiotic therapy for impetigo may be with a topical agent alone or a combination of systemic and topical agents.

Comments: Ozenoxacin belongs to a new generation of non-fluorinated quinolone antibacterial agent, formulated as a topical 1% cream for infectious skin conditions. It is currently under FDA review for the treatment of impetigo in adults and pediatric patients aged 2 months and older. Non-bullous impetigo is more contagious and causes sores that leave a yellow-brown crust once ruptured. Streptococcus and staphylococcus are the primary cause for both bullous and non-bullous impetigo. It is also being evaluated for potential development in a wide range of systemic indications, such as pulmonary infections and bone/joint infections. FDA is expected to rule on the approvability of this product by June 27, 2017.

**semaglutide (Novo Nordisk)**

Current Status: This product is currently under FDA review with an action date of December 05, 2017.

Route of Administration/Dosing: SQ therapy (once weekly).

Proposed Indication(s): Treatment of adults with T2D.

Mechanism of Action: Human GLP-1 analog that stimulates insulin and suppresses glucagon secretion in a glucose-dependent manner.

Patient Impact: According to the CDC, approximately 21 million Americans have been diagnosed with diabetes, which is characterized by high blood sugar levels over a prolonged period.

Current Therapies: Adlyxin™ (lixisenatide - Sanofi), Bydureon® (exenatide extended-release - AZ), Byetta® (exenatide - AZ), Tanzeum® (albiglutide - GSK), Trulicity® (dulaglutide - Lilly), and Victoza® (liraglutide - Novo Nordisk).

Comments: Semaglutide is a once-weekly analog of human GLP-1 that stimulates insulin and suppresses glucagon secretion in a glucose-dependent manner. Novo Nordisk intends to make semaglutide available in a prefilled delivery device based on the same technology platform as FlexTouch. This product will fit into Novo’s current diabetes portfolio adding a once-weekly GLP-1 analog, joining once daily Victoza (liraglutide) and the company’s new once-daily fixed-dose combination, Xultophy (liraglutide / insulin degludec - Novo Nordisk).

**umeclidinium/vilanterol/fluticasone furoate (Closed Triple Combination – GSK / Theravance)**

Current Status: The product is currently under FDA review with an action date of Sept. 21, 2017.

Route of Administration/Dosing: Inhalation (once daily)

Proposed Indication(s): Once-daily inhalation therapy for the maintenance treatment of COPD.

Mechanism of Action: Triple therapy: long-acting muscarinic antagonist (umeclidinium), long-acting beta agonist (vilanterol), and a corticosteroid (fluticasone furoate).

Patient Impact: This product will compete with the other long acting beta2-agonist (LABA), LAMA, corticosteroid and combination inhalers for market share. The availability of a triple combination inhaler could simplify the inhaled drug regimen for some patients with COPD.

Comments: The closed triple therapy is a combination of three molecules: fluticasone furoate (FF), an inhaled corticosteroid (ICS), umeclidinium (UMEC), an anti-cholinergic, also known as a LAMA and vilanterol (VI), a LABA delivered once-daily in GSK’s Elipta® dry powder inhaler. Theravance and GlaxoSmithKline have accelerated the timeline for filing a NDA in the U.S. for the Closed Triple (the combination of fluticasone furoate, umeclidinium, and vilanterol) for patients with COPD. Once available, this product will compete with other inhalers for treating COPD, including the single agent or combination inhaler devices. UPDATE: GSK announces the submission of the NDA on 11/21/2017. Since the products are already available on the market, a 10 month review is anticipated, placing the PDUFA date at about Sep. 21, 2017.
varicella zoster vaccine (Shingrix – GlaxoSmithKline)

Current Status: This product is currently under FDA review with an estimated action date of Oct. 24, 2017.

Route of Administration/Dosing: Two doses are given intramuscularly (IM) two to six months apart.

Proposed Indication(s): Prevention of herpes zoster (shingles) in people aged 50 years and older.

Mechanism of Action: Shingrix is a non-live, recombinant vaccine to help avoid herpes zoster and its complications. It combines glycoprotein E, a protein identified on the varicella zoster virus that causes shingles, with an adjuvant system, AS01B, which aims to improve the immunological response to the antigen.

Patient Impact: Adults 50 years and over are at highest risk for shingles as more than 90% of older adults have been infected with wild type varicella zoster virus.

Current Therapies: Zostavax® (zoster vaccine live - Merck)

Comments: In clinical trials, GSK’s vaccine, Shingrix, remained 90% effective in people over age 70, even four years after injections. Zostavax (zoster vaccine live - Merck) efficacy, by contrast, varies between 18% and 70%, and it declines noticeably in older people. Sales of Merck’s Zostavax, the only shingles vaccine on the market at present, totaled $749 million in 2015. The BLA is backed by data from a Phase III clinical trial, assessing the vaccine’s efficacy, safety and immunogenicity in over 37,000 patients. Based on the timing of GSK’s news releases, the estimated PDUFA date for the product would on or before October 24, 2017 (given a standard FDA review).