

PIPELINE REPORT

Brand Drugs

February 2018



PIPELINE DRUG	CURRENT STATUS	ANTICIPATED APPROVAL	WHAT IS THIS DRUG BEING DEVELOPED FOR?
andexanet alfa (AndexXa -Portola/Bayer)	NDA Filed	2018 02/02/2018 Priority Review	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
brimonidine 0.025% (OTC) (Luminesse - Bausch & Lomb)	NDA Filed	2017 12/27/2017	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
dasotraline (Sunovion)	NDA Filed	2018 08/31/2018	Dual dopamine and norepinephrine reuptake inhibitor (DNRI) for treatment of attention deficit hyperactivity disorder (ADHD); oral therapy
elagolix (ABT-620 - AbbVie/Neurocrine)	NDA Filed	2018 04/27/2018 Priority Review	Oral, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist for treatment of endometriosis-associated pain; oral therapy
epinephrine (Auvi-Q - Kaleo) 0.1mg autoinjector	sNDA Filed	2017 4Q2017 New Indication Priority Review	New 0.1mg strength for use as the first auto-injector approved for use in infants and small children. The needle is size appropriate for smaller patients; subcutaneous therapy
erenumab (Aimovig - Amgen/Novartis)	BLA Filed	2018 05/17/2018	A calcitonin gene-related peptide (CGRP) receptor antagonist monoclonal antibody for prevention of migraine; subcutaneous injection (monthly)
esketamine (Johnson and Johnson)	Phase 3	2019	A small-molecule NMDA receptor antagonist for treatment resistant depression; IV/Intranasal Breakthrough Therapy
fremanezumab (TEV-48125- Teva)	BLA Filed	2018 10/17/2018	Anti-CGRP mAb for the prevention of chronic and high frequency episodic migraines; subcutaneous therapy
glycopyrrolate (PT001 - AstraZeneca)	Phase 3	2018	Inhaled formulation of glycopyrrolate (PT 001), a long-acting muscarinic receptor antagonist (LAMA), for the treatment of chronic obstructive pulmonary disease (COPD)
glycopyrrolate nebulization solution (SUN101 - Sunovion)	NDA Filed	2017 12/15/17	Glycopyrrolate, a long-acting muscarinic antagonist, for treating COPD; nebulization solution

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hydroxyprogesterone caproate (Makena Auto-Injector - AMAG)	sNDA Filed	2018 02/14/2018 New Indication	New auto-injector formulation of Makena to offer a convenient ready-to-administer subcutaneous formulation of the drug. The Orphan Drug Exclusivity (ODE) for Makena expires on Feb. 3, 2018. If approved, this specific drug-device formulation would be protected from direct generic competition for a period of time; subcutaneous therapy
insulin glargine (Lusduna Nexvue -Merck / Samsung Bioepis)	Tentative Approval	2019 Mid 2019	Follow-on insulin glargine product. It will be a brand competitor to Lantus (not a biosimilar); SQ therapy
JZP-110 (Jazz Pharmaceuticals)	Phase 3	2018	Atypical wake-promoting agent designed to treat excessive sleepiness associated with obstructive sleep apnea (OSA) by indirectly enhancing dopaminergic and noradrenergic neurotransmission
levonorgestrel / ethinyl estradiol (Twirla - Agile)	NDA Filed	2017 12/26/2017	Low-dose, weekly contraceptive patch for the prevention of pregnancy. This patch is designed to deliver lower doses of ethinyl estradiol. The patch is applied once weekly for three weeks; transdermal patch
netarsudil ophthalmic solution (Rhopressa - Aerie)	NDA Filed	2018 2/28/2018	Rho Kinase (ROCK) and norepinephrine transporter (NET) inhibitor to lower intraocular pressure (IOP) in patients with glaucoma or ocular hypertension; eye drop (daily)
testosterone undecanoate (Jatenzo -Clarus)	NDA Filed	2017 12/26/2017	Jatenzo is a testosterone prodrug for testosterone replacement therapy in men with low testosterone level. The product is dosed twice-daily; oral therapy
testosterone undecanoate (LPCN 1021 - Lipocine)	NDA Filed	2018 2/08/2018	LPCN 1021 (testosterone prodrug) is a twice-daily oral testosterone replacement therapy for treating hypo gonadal men with low testosterone; oral therapy (twice daily)

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andexanet alfa (AndexXa - Portola/Bayer)

Current Status: This product is currently under FDA review with an action date of Feb. 2, 2018.

Route of Administration/Dosing: Intravenous (IV) therapy

Proposed Indication(s): Universal Factor Xa 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 haemostasis.

Patient Impact: One of the major drawbacks to the new oral anticoagulants (Factor Xa inhibitors) is that a reversal agent is currently not available. Annually, around 1-4% of patients treated with Factor Xa 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 2/3 (2018)

Comments: Potential first-in-class recombinant modified Factor Xa molecule that is being developed as an antidote for patients receiving a Factor Xa inhibitors (e.g. Bevyxxa, Eliquis, Savaysa, and Xarelto) who suffer a major bleeding episode or who may require emergency surgery. As there are no specific reversal agents for factor Xa inhibitors yet, andexanet alfa could potentially address an unmet need. 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 factor Xa inhibitors or LMWH for other medical conditions. Andexanet alfa is a recombinant protein that is structurally distinct from native factor Xa, and acts as a decoy for factor Xa inhibitors in the blood. This prevents the drugs from inhibiting the activity of native factor Xa, thereby allowing native factor Xa to participate in restoring hemostasis. The drug does not seem to be effective against the factor IIa inhibitor, Pradaxa (dabigatran – BI). 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-Factor Xa activity (>90 percent reduction of mean anti-Factor Xa activity within five minutes of the end of administration) compared with placebo (p<0.0001). AndexXa is an important option for patients receiving factor Xa inhibitors who experience a major bleeding event or require emergency surgery. There are currently no licensed reversal agents for any factor Xa inhibitor. 11/11/2015: Portola released positive top-line data from the second part of AndexXa's Phase 3 ANNEXA-R trial. The study demonstrated that administration of an intravenous 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. Portola has initiated a rolling BLA submission and expects to complete it by the end of 2015. 03/04/2016 - FDA has accepted the application, with a PDUFA date of 08/17/2016. 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 Pharmaceuticals Enters into \$50 Million Loan Agreement with Bristol-Myers Squibb and Pfizer for Continued Development of AndexXa™ (andexanet alfa). Portola expects to resubmit the BLA in 2017. Aug 2017 update: FDA has accepted the resubmission of the BLA. **The product currently has an FDA action date of 02/02/2018.**

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): Non-prescription (OTC) treatment of ocular redness

Mechanism of Action: Brimonidine is an alpha adrenergic receptor agonist

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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.

Current Therapies: Over-the-counter (OTC) products for treating red eyes (e.g. Clear Eyes and Visine)

Comments: Luminesse™ is a topical vasoconstrictor formulation to be used Over-the-Counter (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 Luminesse 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 postmarketing 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 (tolerance or loss of effectiveness) and rebound congestion, which are both common to currently available OTC redness reliever eye drops. Bausch + Lomb announced that the FDA has accepted the New Drug Application (NDA) for brimonidine tartrate ophthalmic solution, 0.025% (Luminesse), and set a PDUFA action date of December 27, 2017

dasotraline (Sunovion)

Current Status: This product is currently under FDA review with an action date of Aug. 31, 2018

Route of Administration/Dosing: Oral therapy (once daily)

Proposed Indication(s): Treating attention deficit hyperactivity disorder (ADHD)

Mechanism of Action: Dual dopamine and norepinephrine reuptake inhibitor (DNRI)

Patient Impact: Attention deficit hyperactivity disorder (ADHD) is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning and development, as characterized by inattention (e.g., distractibility, forgetfulness) and/or hyperactivity and impulsivity (e.g., fidgeting, restlessness). Approximately 11 percent of children four to 17 years of age have been diagnosed with ADHD in the United States. Up to 60 percent of children with ADHD continue to experience symptoms into adulthood. It is estimated that 4.4 percent of adults between ages 18 and 44 years' experience some symptoms and disabilities from ADHD in the U.S.

Current Therapies: Several formulations of the following drugs are available, many of which are also available generically: amphetamine, methylphenidate, mixed salts of single-entity amphetamine, atomoxetine, guanfacine and lisdexamfetamine.

Comments: Dasotraline is a new chemical entity that is considered to be a dopamine and norepinephrine reuptake inhibitor (DNRI). It has an extended half-life (47-77 hours) that supports the potential for plasma concentrations yielding a continuous therapeutic effect over the 24-hour dosing interval at steady state. Dasotraline has shown a lower potential for abuse than methylphenidate in clinical testing. Dasotraline was discovered by Sunovion Pharmaceuticals Inc. and is currently in development to evaluate its use in treating ADHD in adults and children, and BED in adults in the United States. The NDA submission is supported by data from the clinical program for dasotraline in ADHD, which included four placebo-controlled safety and efficacy studies, as well as two long-term studies that assessed the safety of dasotraline in patients with ADHD for up to one year. In total, approximately 2,500 patients with ADHD were evaluated in these studies utilizing dasotraline dosages in the range of 2 mg/day to 8 mg/day. Dasotraline was generally well tolerated. Dasotraline is also being investigated for the treatment of binge eating disorder (BED) in adults. If approved, this product will be another treatment option for patients with ADHD. It is currently under FDA review with an estimated action date (PDUFA) of Aug. 31, 2018.

elagolix (ABT-620 - AbbVie/Neurocrine)

Current Status: This product is currently under FDA review with an action date of Sept. 6, 2018

Route of Administration/Dosing: Oral therapy (150mg once daily and 200mg twice daily have been investigated)

Proposed Indication(s): Management of pain associated with endometriosis

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Mechanism of Action: An orally administered gonadotropin-releasing hormone (GnRH) receptor antagonist that blocks endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration results in readily reversible, dose-dependent inhibition of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, leading to reduced ovarian production of the sex hormones, estradiol and progesterone, while on therapy.

Patient Impact: Endometriosis occurs when tissue similar to that normally found in the uterus begins to grow outside of the uterus, leading to long-term pelvic pain (during or between periods), pain with intercourse and other painful symptoms. There is no cure for endometriosis and the associated pain is currently managed with oral contraceptives, progestin, danazol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and GnRH agonists, many of which are not specifically indicated for the treatment of endometriosis. It has been estimated that that about 5% to 10% of women in their reproductive years suffer from disabling bouts of this ailment.

Comments: Elagolix (ABT-620) is an oral gonadotropin-releasing hormone antagonist being studied for the treatment of endometriosis and uterine fibroid. On Sept. 6, 2017, AbbVie announced the submission of the New Drug Application (NDA). The NDA is supported by data from the largest prospective randomized endometriosis clinical trials conducted to date, which evaluated the safety and efficacy of elagolix in nearly 1,700 women with moderate-to severe endometriosis-associated pain. The data from two replicate Phase 3 studies demonstrated that, at month three and month six, both elagolix doses (150 mg once daily and 200 mg twice daily) resulted in a statistically significant higher proportion of responders for menstrual pain (dysmenorrhea) and non-menstrual pelvic pain associated with endometriosis as measured by the Daily Endometriosis Pain Impact scale versus placebo. Significant improvements compared to placebo were also observed at month three for the 200 mg twice daily dose in scores for painful intercourse (dyspareunia). A reduction in the amount and frequency of rescue pain medication use, including nonsteroidal anti-inflammatory drugs and opioids, compared to placebo was also seen in the higher dose at month three and six. In clinical studies, elagolix treatment decreased endometrial proliferation in a dose-dependent manner after six months of treatment with no adverse endometrial findings. Phase 3 trials of elagolix for the management of uterine fibroids are ongoing.

epinephrine (Auvi-Q - Kaleo) 0.1mg autoinjector

Current Status: This product is currently under FDA review with an action date sometime in the fourth quarter of 2017

Route of Administration/Dosing: This is a new 0.1mg strength of Auvi-Q, a subcutaneously administered formulation of epinephrine

Proposed Indication(s): New 0.1mg dose and auto-injector with shorter needle length to deliver the treatment, for treatment of anaphylaxis in infants and small children weighing 16.5 to 33 lbs.

Mechanism of Action: Through its action on alpha-adrenergic receptors, epinephrine lessens the vasodilation and increased vascular permeability that occurs during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension.

Patient Impact: Anaphylaxis is a serious allergic reaction that happens quickly and may cause death. Anaphylaxis can occur as a result of exposure to allergens including tree nuts, peanuts, milk, eggs, fish, shellfish, soy, wheat, insect bites, latex and medication, among other allergens.

Current Therapies: EpiPen (epinephrine - Mylan/authorized generic) and an authorized generic to Adrenaclick (Impax/Ameda) [brand Adrenaclick has been discontinued]

Comments: The AUVI-Q 0.1 mg Auto-injector not only contains a dose of epinephrine tailored to infants and small children, but contains important product features such as an optimized needle length designed to help mitigate the risk of striking bone in this population. If approved, the new AUVI-Q 0.1 mg Auto-injector is projected to be available for patients in the first half of 2018. This new strength could offer new marketing opportunities for this company. However, this product is significantly more expensive (\$4,500 WAC) than other available epinephrine autoinjector products

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erenumab (Aimovig - Amgen/Novartis)

Current Status: PDUFA date: May 17, 2018

Route of Administration/Dosing: Subcutaneous (SC) therapy (once monthly)

Proposed Indication(s): For the prevention of migraine in patients experiencing at least four migraine days per month

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: Migraine impacts approximately 12% of the US population – approximately 18% of women and 6% of men. In clinical practice, experts suggest considering preventative therapies in patients who have four or more migraine attacks per month, or are overusing acute medication, or who experience significant disability for migraine. It is estimated that approximately 3.5 million patients in the U.S. use medications that prevent/reduce migraine frequency/severity. Amgen estimates that the majority of patient on preventative therapy are receiving first-line therapy (55%) and would not be the target population for erenumab. Up to 1.6 million Americans may be candidates for CGRPs.

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

Pipeline Product(s): fremanezumab (TEV-48125 - Teva) - Oct. 17, 2018; galcanezumab (LY2951742 - Lilly) - 2018; eptinezumab (ALD403 - Adler) - 2019; ubrogepant (MK-1602 - Allergan) - 2020

Comments: Erenumab is a novel migraine treatment that targets the calcitonin-gene-related-peptide (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). Amgen’s product is slightly different as it targets the CGRP receptor, whereas the other three products directly target circulating CGRP. All four compounds have initiated phase 3 development in what is becoming an increasingly crowded market. On July 20, 2017, Amgen announced that the U.S. FDA has accepted for review the Biologics License Application for Aimovig (erenumab) for the prevention of migraine in patients experiencing four or more migraine days per month. The FDA has set a Prescription Drug User Fee Act target action date of May 17, 2018. Aimovig will be jointly commercialized in the U.S. by Amgen and Novartis. On Sept. 7, 2017, Amgen announced data from a pre-planned sub-analysis from the pivotal Phase 2 chronic migraine study, demonstrating that Aimovig reduced the number of monthly migraine days (MMDs) in patients who have failed previous preventive therapies. Additionally, results from a study in patients with stable angina adds further support to the safety profile of Aimovig. Studies have shown that up to 80 percent of people with migraine discontinue preventive treatment within one year. In a pre-specified sub-analysis from the Phase 2 study, Aimovig showed benefits for people with chronic migraine who have previously tried and failed preventive treatments. At the end of the 12-week study, patients who had failed two or more prior preventive treatments experienced a reduction of 7.0 days and 5.4 days in the Aimovig 140 mg and 70 mg, respectively, compared to placebo reduction of 2.7 days ($p < 0.001$). Furthermore, in the Aimovig treated arms, the odds of cutting migraine days in at least half was three-to-four fold higher than in the placebo arm (140 mg: 41.3 percent, 70 mg: 35.6 percent, placebo: 14.2 percent ($p < 0.001$ for change from baseline in exercise time was -11.0 seconds (90 percent confidence interval $-44.9, 22.9$). In addition, no significant differences were seen between the two groups in time to onset of angina or time to onset of electrocardiogram change consistent with onset of myocardial ischemia. Adverse events were reported in 27 percent of patients receiving Aimovig and in 32 percent of patients receiving placebo. The most frequent treatment-emergent adverse events (reported in >2 percent of patients) were headache (4.5 percent) and viral upper respiratory infection (4.5 percent) in the Aimovig group, and were hypotension (4.5 percent), influenza (4.5 percent) and viral infection (4.5 percent) in the placebo group. both doses versus placebo). The safety profile of Aimovig was similar to placebo across both treatment arms in the Phase 2 study. No adverse event was reported in greater than five percent of patients treated with Aimovig; the most common adverse events were injection site pain, upper respiratory tract infection and nausea. Aimovig was tested in a group of patients with stable angina due to coronary artery disease. A treadmill “stress test” is often used to

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gauge how well a patient's heart can handle exercise. The study met its primary endpoint of non inferiority, showing no difference in exercise time among participants receiving Aimovig or placebo. The treatment difference in mean change from baseline in exercise time was -11.0 seconds (90 percent confidence interval -44.9, 22.9). In addition, no significant differences were seen between the two groups in time to onset of angina or time to onset of electrocardiogram change consistent with onset of myocardial ischemia. Adverse events were reported in 27 percent of patients receiving Aimovig and in 32 percent of patients receiving placebo. The most frequent treatment-emergent adverse events (reported in >2 percent of patients) were headache (4.5 percent) and viral upper respiratory infection (4.5 percent) in the Aimovig group, and were hypotension (4.5 percent), influenza (4.5 percent) and viral infection (4.5 percent) in the placebo group.

esketamine (Johnson and Johnson)

Current Status: Phase 3

Route of Administration/Dosing: Intranasal formulation of esketamine

Proposed Indication(s): Treatment of major depressive disorder with imminent risk for suicide

Mechanism of Action: Esketamine is a non-competitive and subtype non-selective activity-dependent N-methyl-D-aspartate (NMDA) receptor antagonist, which has a novel mechanism of action, meaning it works differently than currently available therapies for depression.

Patient Impact: Major depressive disorder affects approximately 16 million people in the U.S. Also, in the U.S., there are more than 41,000 suicides each year, many of which result from untreated or poorly treated major depression. Only 30 percent of patients on currently available antidepressants achieve remission.

Comments: This product has received "breakthrough" status by FDA for major depressive disorder with imminent risk for suicide. There is a critical need for drugs that can interrupt the thought processes that can lead to suicide in patients with severe depression, particularly as most currently-used antidepressants can take weeks to have an effect. Currently the only approved fast-acting treatments for MDD are transcranial magnetic stimulation and electroconvulsive therapy. According to J&J, there are more than 41,000 suicides each year in the US, many of which result from untreated or poorly treated major depression. The suicide rate in MDD patients is approximately 20 times higher than in the general population. Filing with FDA will likely occur in 2018 with final approval in late 2018/2019.

fremanezumab (TEV-48125 - Teva)

Current Status: This product is currently under FDA review with an action date of October 17, 2018

Route of Administration/Dosing: 225 mg or 675 mg administered once-monthly. Product also studied as a quarterly injection; subcutaneous therapy.

Proposed Indication(s): Prevention of chronic and high frequency episodic migraines'

Mechanism of Action: Fully human monoclonal antibody under investigation for the prevention of migraine. Fremanezumab specifically targets the Calcitonin-Gene-Related-Peptide (CGRP), which is believed to transmit signals that can cause incapacitating pain.

Patient Impact: Migraine impacts approximately 12% of the US population – approximately 18% of women and 6% of men. In clinical practice, experts suggest considering preventative therapies in patients who have four or more migraine attacks per month, or are overusing acute medication, or who experience significant disability for migraine. It is estimated that approximately 3.5 million patients in the U.S. use medications that prevent/reduce migraine frequency/severity. Amgen estimates that the majority of patients on preventative therapy are receiving first-line therapy (55%) and would not be the target population for erenumab. Up to 1.6 million Americans may be candidates for CGRPs.

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

Pipeline Product(s): Amgen's erenumab is a monthly SC CGRP inhibitor that is expected to be approved May 17, 2018. galcanezumab (LY2951742 - Lilly) - 2018; eptinezumab (ALD403 - Adler) - 2019; ubrogepant (MK-1602 - Allergan) – 2020

Comments: Fremanezumab is a novel migraine treatment that targets the calcitonin-gene-related-peptide (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. The majority of pipeline drugs, including Teva's fremanezumab, bind to CGRP inhibiting its action. Amgen's product, which is slightly different as it targets the CGRP receptor, is the lead product. Lilly's galcanezumab and Teva's fremanezumab are close behind. All of these products are administered via subcutaneous injection. Fremanezumab has a longer half-life than other near-term pipeline agents allowing for possible quarterly administration. The BLA includes data from the HALO clinical trial program, which enrolled more than 2,000 patients with episodic migraine (EM) and chronic migraine (CM), evaluating both monthly and quarterly dose regimens of fremanezumab. Results from these trials were recently presented at the Congress of the International Headache Society (IHC) in September and will be published in future peer-reviewed publications. Across the Phase III HALO studies in chronic and episodic migraine, fremanezumab achieved statistically significant and clinically meaningful results for all 25 primary and secondary analyses in both monthly and quarterly dosing regimens. In the chronic migraine study, endpoint analyses presented at IHC include: Significant reduction in the number of monthly headache days of at least moderate severity during the 12-week period after 1st dose for both dosing regimens [monthly (-4.6 days) and quarterly (-4.3 days) versus placebo (-2.5 days); $p < 0.0001$]; Statistically significant reduction in the number of monthly migraine days during the 12-week period after the 1st dose, for both dosing regimens [monthly (-5.0 days from a baseline of 16.0 days) and quarterly (-4.9 days from a baseline of 16.2 days) versus placebo (-3.2 days from a baseline of 16.3 days); $p < 0.0001$], and during the 4-week period after 1st dose, for both dosing regimens ($p < 0.0001$); Improvement in Migraine-Specific Quality of Life scores for both dosing regimens [least-squares mean ffl standard error differences versus placebo: monthly (6.3ffl1.4) and quarterly (5.6ffl1.4); $p < 0.0001$]; Improvement in overall health status as measured by the EuroQol 5-dimension 5 response level (EQ-5D-5L) questionnaire for both dosing regimens [quarterly (4.6ffl1.1; $p = 0.0402$) and monthly (4.8ffl1.1; $p = 0.0291$) versus placebo (2.2ffl1.1)]; Significant reduction in the weekly number of headache days of at least moderate severity at week 1 (-1.1 days; $p < 0.0001$) versus placebo (-0.5 days). In episodic migraine, endpoint analyses presented at IHC include: Reduction in the number of monthly migraine days during the 12-week period for both dosing regimens [monthly (-3.7 days from a baseline of 9.2 days) and quarterly (-3.4 days from a baseline of 8.9 days) versus placebo (-2.2 days from a baseline of 9.1 days); $p < 0.0001$] and during the 4-week period after 1st dose, for both dosing regimens; Reduction in the number of monthly headache days of at least moderate severity during the 12-week period for both dosing regimens [monthly (-2.9 days) and quarterly (-3.0 days); vs placebo (-1.5 days); $p < 0.0001$] and during the 4-week period after 1st dose, for both dosing regimens ($p < 0.0001$); Significant reduction in the number of monthly days of acute headache medication use for both [monthly (-3.0 days) and quarterly (-2.9 days versus placebo (-1.6 days)); $p < 0.0001$]; A #50% reduction in monthly average number of migraine days of least moderate severity for both dosing regimens [monthly (47.7%) and quarterly (44.4%) versus placebo (27.9%); $p < 0.0001$]; Improvement in disability as measured by the Migraine Disability Assessment (MIDAS) for both dosing regimens [monthly (-24.6; $p = 0.0021$) and quarterly (-23.0; $p = 0.0023$) versus placebo (-17.5)]. The most common adverse events reported in clinical trials include injection site induration, erythema, and pruritus. . On Oct. 17, 2017, Teva announced the submission of the biologics license application (BLA) for fremanezumab to U.S. The estimated PFUDA date is Oct. 17, 2018 (12 month review).

glycopyrrolate (PT001 - AstraZeneca)

Current Status: Phase 3

Route of Administration/Dosing: Inhalation therapy

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

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

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Patient Impact: Thirty million patients in the U.S. suffer from COPD, with 6MM receiving treatment. Combivent (albuterol/atrovent - BI) requires four times daily administration. A LAMA and a LABA can be administered individually for management of the disease.

Comments: Pearl Therapeutics (a subsidiary of AstraZeneca) is developing an inhaled formulation of glycopyrrolate (PT001), a long-acting muscarinic receptor antagonist (LAMA), for the treatment of chronic obstructive pulmonary disease (COPD) and asthma. Antagonists of the muscarinic receptor inhibit cholinergic transmission, thereby relieving airway constriction. Pearl's drug candidates are being developed for use with a metered dose inhaler (MDI), using advanced particle technologies licensed from Nektar Therapeutics. These technologies utilize porous particles to create stable suspensions in hydrofluoroalkane propellants, producing high performance aerosols upon actuation.

glycopyrrolate nebulization solution (SUN101 - Sunovion)

Current Status: This product is currently under FDA review with an action date of December 15, 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 chronic obstructive pulmonary disease (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 United States.

Comments: Nebulizer formulation of the long-acting muscarinic antagonist (LAMA) for delivery via Sunovion's investigational eFlow electronic closed nebulizer system for long-term maintenance treatment of adults with moderate to very severe chronic obstructive pulmonary disease (COPD). The product will be administered using the company's proprietary nebulizer system called eFlow. 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. FDA issued a Complete Response letter for this product in May 2017. The company has resubmitted the applications,

hydroxyprogesterone caproate (Makena Auto-Injector - AMAG)

Current Status: This product is currently under FDA review with an action date of February 14, 2018

Proposed Indication(s): Subcutaneous (SQ) Therapy (auto-injector device)

Mechanism of Action: Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known.

Patient Impact: Twelve percent of all births in the U.S. are premature. Predisposing risk factors for preterm delivery include a documented history of a previous singleton preterm delivery after less than 37 weeks of gestation, multiple gestations, short cervical length, body weight less than 50 kg (110 pounds), bleeding, and African-American ancestry. According to the March of Dimes, one in eight births in the U.S. is premature, which equates to the need for treatment of nearly 200,000 mothers.

Comments: Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity. The company believes that, if approved, this drug-device combination product can help meet the needs of

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providers by offering the convenience of a ready-to administer subcutaneous auto-injector while providing patients with an alternative option to an intramuscular injection. This is in attempt to maintain market share after the Orphan Drug Exclusivity (ODE) for Makena expires on Feb. 3, 2018. After this date, generic manufacturers are expected to receive FDA approval for the standard formulation of Makena.

insulin glargine (Lusduna Nexvue - Merck / Samsung Bioepis)

Current Status: "tentative approval"

Route of Administration/Dosing: Subcutaneous (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 the Lantus (100 units/ml)

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 type 2 diabetes by 2014. In the US, basal insulin market is estimated at more than \$6

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 US 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 US, while in Europe the drugs are considered biosimilars. At 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. 07/24/2017: FDA granted "tentative approval" for Merck's Lusduna Nexvue. Merck and Sanofi (innovator company and marketer of Lantus) are involved in patent litigation. Unless litigation is resolved, FDA cannot grant final approval of Merck's Lusduna Nexvue until the 30 month stay expires in Mid-2019.

JZP-110 (Jazz Pharmaceuticals)

Current Status: Phase 3

Route of Administration/Dosing: Oral therapy

Proposed Indication(s): Treatment of adult patients with excessive sleepiness (ES) associated with narcolepsy and obstructive sleep apnea (OSA).

Mechanism of Action: JZP-110 is a selective dopamine and norepinephrine reuptake Inhibitor (DNRI).

Patient Impact: Jazz Pharmaceuticals (JAZZ) estimates that approximately 6.0 million people in the US suffer from obstructive sleep apnea or excessive sleeping, while about 60,000 are affected by narcolepsy, and ~850,000 suffer from Parkinson's disease. Many patients seeking treatment switch to second-line, third-line, or fourth-line of drugs due to dissatisfaction with existing regimens.

Current Therapies: Amphetamines, Provigil (modafinil - Teva/generics) and Nuvigil (armodafinil - Teva/generics)

Comments: JZP-110 has the potential to be a differentiated, best-in-class treatment. The data suggest that, at higher doses, JZP-110 is more effective than Provigil and Nuvigil, with the usual caveats about cross-trial comparisons. Provigil has shown a placebo-adjusted increase in maintenance of wakefulness test (MWT) of around 3 minutes, according to its label, versus 7.7-12.8 minutes with

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the 150mg and 300mg doses of JZP-110, varying by indication. The most common adverse events with JZP-110 are insomnia, headache, nausea, diarrhea, decreased appetite, and anxiety. JZP-110 looks to provide a more efficacious result than currently-marketed stimulants, and therefore Jazz is not concerned about potentially launching it into a genericized market. Unlike Provigil and Nuvigil, JZP110 is not metabolized through the liver, and as a result, it should not interfere with oral contraceptives. The company expects to target severe narcolepsy and obstructive sleep apnea (OSA) patients and therefore does not anticipate significant pushback from payers. The company is planning to file for approval before the end of the year (2017) with FDA approval possible by the end of 2018 (12 months from submission for a standard review).

levonorgestrel / ethinyl estradiol (Twirla - Agile)

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

Route of Administration/Dosing: Transdermal patch applied weekly for three weeks, followed by a patch free week.

Proposed Indication(s): Low dose contraceptive patch for the prevention of pregnancy

Mechanism of Action: Levonorgestrel binds to the progesterone receptor in the nucleus of target cells, thereby stimulating the resulting hormone-receptor complex, initiating transcription, and increasing the synthesis of certain proteins. This results in a suppression of luteinizing hormone (LH) activity and an inhibition of ovulation, as well as an alteration in the cervical mucus and endometrium. Target cells include the female reproductive tract, the mammary gland, the hypothalamus and the pituitary. Once bound to the receptor, progestins like levonorgestrel will slow the frequency of release of gonadotropin releasing hormone (GnRH) from the hypothalamus and blunt the pre-ovulatory LH (luteinizing hormone) surge. Ethinyl estradiol is an estrogen receptor agonist. Estradiol (a form of estrogen) is a female sex hormone necessary for many processes in the body. LH and FSH play key roles in the development of the egg and preparation of the lining of the uterus for implantation of the embryo.

Patient Impact: There are an estimated 61 million women in their childbearing years in the US. About 43 million (70%) are at risk of unintended pregnancy. A contraceptive patch will provide another contraceptive method for these individuals.

Comments: Low-dose, weekly contraceptive patch for the prevention of pregnancy. This patch is designed to deliver lower doses of ethinyl estradiol (EE). The patch is applied once weekly for three weeks followed by a fourth, patch-free week. The patch may be applied to the abdomen, buttocks, or upper torso, is soft and flexible with a cloth-like, silky feel, and designed to provide excellent adhesion, comfort, and appearance. Twirla will administer a low estrogen dose through a transdermal patch (defined as 30mcg or less). Twirla delivers a low estrogen dose, equivalent of 30 micrograms of EE, whereas JNJ's Ortho Evra delivers 35mcg of EE. Agile resubmitted the NDA in response to a February 2013 "Complete Response" Letter from the FDA, which recommended that Agile conduct a new clinical trial and provide additional information on the manufacturing process for Twirla.

netarsudil ophthalmic solution (Rhopressa - Aerie)

Current Status: This product is currently under FDA review with an action date of February 28, 2018

Route of Administration/Dosing: Ophthalmic Therapy (once-daily administration)

Proposed Indication(s): Ophthalmic therapy (once-daily)

Mechanism of Action: Netarsudil is a novel, once daily, ophthalmic solution designed to lower intraocular pressure via three different mechanisms. It increases fluid outflow through the trabecular meshwork by inhibiting Rho Kinase (ROCK), reduces fluid production in the eye by inhibiting norepinephrine transporter (NET), and lowers episcleral venous pressure.

Patient Impact: It is estimated that more than 3 million patients in the U.S. have open angle glaucoma and ocular hypertension

Comments: Rhopressa is a novel, once daily, ophthalmic solution designed to lower intraocular pressure via three different mecha-

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nisms. It increases fluid outflow through the trabecular meshwork by inhibiting Rho Kinase (ROCK), reduces fluid production in the eye by inhibiting norepinephrine transporter (NET), and lowers episcleral venous pressure. The company is also working on a fixed dose combination, called Roclatan (netarsudil/latanoprost ophthalmic solution 0.02%/0.005%), which is a fixed-dose combination of Rhopressa with the latanoprost. Rhopressa could represent another treatment option for patients who are not adequately controlled by available therapies. This product is currently under FDA review with an action date of February 28, 2018. FDA's review concluded the drug reduced elevated intraocular pressure in the eye. But the review also noted that the comparator drug, the generic timolol ophthalmic solution 0.5% twice daily, was more effective for the more severely afflicted patients

testosterone undecanoate (Jatenzo - Clarus)

Current Status: This product is currently under FDA review with an action date of December 26, 2017

Route of Administration/Dosing: Twice daily oral therapy. The recommended dose is 200 mg of T twice daily and can be adjusted by increments of 50 mg on subsequent doses to between 100 mg and 300 mg, twice daily.

Proposed Indication(s): testosterone replacement therapy

Mechanism of Action: testosterone replacement therapy

Patient Impact: An oral testosterone replacement product would not only be convenient, but would avoid many of the safety issues associated with accidental transfer of testosterone to women or children that can occur from transdermal products.

Cost Estimate:

Current Therapies: Injectable and topical testosterone. Oral products also available, but less commonly used due to adverse effects.

Comments: Jatenzo is testosterone undecanoate, a prodrug of testosterone formulated for oral administration for testosterone replacement therapy. The bioavailability of testosterone is low (4-7% in literature). Testosterone undecanoate is a fatty-acid ester prodrug allowing the drug to be absorbed via intestinal lymphatics, reducing first pass hepatic effect. Hydrolysis of the drug occurred by esterase's primarily in the blood and liver. Currently available oral testosterone formulations, methyl testosterone, are reported to have liver safety issues. This product is currently under FDA review with a December 26, 2017 action date.

testosterone undecanoate (LPCN 1021 - Lipocine)

Current Status: This product is currently under FDA review with an action date of February 08, 2018

Route of Administration/Dosing: Oral therapy

Proposed Indication(s): Twice-daily oral formulation of testosterone for replacement therapy in adult men with hypogonadism

Mechanism of Action: Human Testosterone replacement therapy

Patient Impact: An oral testosterone replacement product would not only be convenient, but would avoid many of the safety issues associated with accidental transfer of testosterone to women or children that can occur from transdermal products.

Cost Estimate:

Current Therapies: AdlyxInjectable and topical testosterone. Oral products also available, but less commonly used due to adverse effects.

Comments: Tlando (LPCN1021) is testosterone undecanoate, a prodrug of testosterone formulated for oral administration for testosterone replacement therapy. The bioavailability of testosterone is low (4-7% in literature). Testosterone undecanoate is a fatty-acid ester prodrug allowing the drug to be absorbed via intestinal lymphatics, reducing first-pass hepatic effect. Hydrolysis of the drug occurred by esterases primarily in the blood and liver. Currently available testosterone formulations, methyl testosterone, is reported to have liver safety issues. This product is currently under FDA review with a June 28, 2016 action date. A CRL was issued in Oct. 2017. Update: FDA plans to discuss the New Drug Application (NDA) submitted at an advisory committee meeting, although the has not been finalized but will occur prior to the PDUFA goal date of February 8, 2018.