

PIPELINE REPORT

Brand Drugs

July 2018



PIPELINE DRUG	CURRENT STATUS	ANTICIPATED APPROVAL	WHAT IS THIS DRUG BEING DEVELOPED FOR?
bremelanotide (Rekynda - Palatin Technologies)	NDA Filed	2019 03/26/2019	Melanocortin 4 receptor agonist for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women; subcutaneous injection with a pre-filled autoinjector pen
buprenorphine SL spray (INSYS)	NDA Filed	2018 07/28/2018	Novel formulation of buprenorphine (sublingual spray) for the management of moderate-to-severe acute pain; sublingual spray
cyclosporine A ophthalmic soln (OTX-101 - Sun)	NDA Filed	2018 08/27/2018	A novel nanomicellar formulation of cyclosporine A 0.09% ophthalmic solution for treating dry eyes syndrome; ophthalmic therapy
dasotraline (Sunovion)	NDA Filed	2018 08/31/2018	Dual dopamine and norepinephrine reuptake inhibitor (DNRI) for treating attention deficit hyperactivity disorder (ADHD); oral therapy
elagolix (ABT-620 - AbbVie/Neurocrine)	NDA Filed	2018 08/6/2018 Priority Review	Oral, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist for treating endometriosis-associated pain; oral therapy
erenumab (Aimovig - Amgen/Novartis)	BLA Filed	2018 APPROVED 05/17/2018	A calcitonin gene-related peptide (CGRP) receptor antagonist monoclonal antibody for prevention of migraine in patients with four or more migraine days per month; subcutaneous injection (monthly)
estradiol softgel capsule (Yuvvexy - TherapeuticsMD)	NDA Filed	2018 05/29/2018	Applicator-free, vaginal, estradiol softgel capsule being proposed for the treatment of moderate-to-severe vaginal pain during sexual intercourse (dyspareunia), a symptom of vulvar and vaginal atrophy (VVA) due to menopause; vaginal capsule
fremanezumab (Teva)	BLA Filed	2018 06/16/2018 Priority Review	Anti-CGRP mAb for the prevention of chronic and high frequency episodic migraines; subcutaneous therapy
galcanezumab (Lilly)	Phase 3	2018 10/11/2018	A once-monthly, subcutaneously administered monoclonal antibody that neutralizes calcitonin gene-related peptide (CGRP) for the prophylaxis of migraine headaches; subcutaneous injection
glycopyrronium tosylate (DRM04 -Dermira)	NDA Filed	2018 06/30/2018	Topical anticholinergic product for treatment of severe hyperhidrosis; topical 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); subcutaneous therapy

PIPELINE REPORT

Brand Drugs

July 2018



PIPELINE DRUG	CURRENT STATUS	ANTICIPATED APPROVAL	WHAT IS THIS DRUG BEING DEVELOPED FOR?
insulin glargine (Semglee Mylan/Biocon)	NDA Filed	2018 July 2018	Biosimilar to Lantus; subcutaneous therapy
lofexidine (Lucemyra – US WorldMeds)	Tentative Approval	2018 FDA APPROVED 05/16/2018	Selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine to reduce the severity of withdrawal symptoms in patients experiencing opioid withdrawal; oral
oxycodone, extended-release (Remoxy - Pain Therapeutics)	NDA Filed	2018 08/7/2018 Priority Review	Abuse-resistant long-acting (twice daily) oral formulation of oxycodone for round-the-clock treatment of persistent pain- when crushed, the Remoxy gel-cap yields a viscous gel presumably too thick to snort or inject; oral therapy
prucalopride (Resolor - Shire)	NDA Filed	2018 12/21/2018	A 5-HT4 receptor agonist- 5-HT4 receptors are mainly found in the gut wall and are involved in the stimulation of high amplitude contractions and coordination of bowel motility; oral therapy
sarecycline (Seysara - Allergan / Paratek)	NDA Filed	2018 10/20/2018	Narrow spectrum tetracycline-derived antibiotic with anti-inflammatory properties for use as an oral treatment of moderate to severe acne vulgaris in patients 9 years of age and older; oral therapy
sodium zirconium cyclosilicate (ZS9 - AstraZeneca)	NDA Filed	2018 2Q:2018	Non-absorbed zirconium silicate designed to preferentially trap potassium ions for the treatment of hyperkalemia; oral (once daily)
solriamfetol (JZP-110 - Jazz Pharmaceuticals)	NDA Filed	2018 12/20/2018	Dopamine and norepinephrine reuptake inhibitor (DNRI) for the treatment of excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA); oral
sotagliflozin (Lexicon / Sanofi)	NDA Filed	2019 03/16/2019	A dual SGLT1 and SGLT2 inhibitor for use in combination with insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus; oral therapy
ulipristal acetate (Esmya - Allergan)	NDA Filed	2018 August 2018	Progesterone agonist/antagonist for the treatment of abnormal uterine bleeding in women with uterine fibroids; oral therapy

PIPELINE REPORT

Brand Drug Detail - July 2018



bremelanotide (Rekynda - Palatin Technologies)

Current Status: This product is currently under FDA review with an action date of March 26, 2019

Route of Administration/Dosing: Subcutaneous (SC) therapy; twice daily

Proposed Indication(s): Treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women

Mechanism of Action: Bremelanotide is a peptide melanocortin receptor agonist which targets the endogenous pathways involved in sexual desire and arousal.

Patient Impact: Hypoactive sexual desire disorder (HSDD) is a lack of sexual desire or interest that also causes personal distress. HSDD is the most common of the female sexual dysfunctions (FSD), affecting 1 in 10 women. HSDD is the most common type of FSD affecting an estimated 12 million women in the United States.

Current Therapies: Addyi (flibanserin - Valeant)

Comments: In March 2018, AMAG Pharmaceuticals filed a New Drug Application (NDA) with the US FDA for bremelanotide subcutaneous self-injection (a prefilled auto-injector pen) for the treatment of female sexual dysfunction (hypoactive sexual desire disorder), in pre-menopausal women. The submission was supported by the data from two phase III RECONNECT trials. Female sexual dysfunction, or FSD, is a multifactorial condition that has anatomical, physiological, medical, psychological and social components. It is defined as persistent or recurring problems during one or more of the stages of sexual response, which cause distress or problems to the women. It is related to problems of sexual desire, arousal, orgasm and pain. In females suffering from sexual dysfunction, specifically premenopausal, bremelanotide is effective in helping women achieve the drive they need to partake in sexual interactions. If approved, this new treatment will be available as a subcutaneous self-injection in a prefilled disposable auto-injector pen for use in anticipation of a sexual encounter. Women with HSDD using bremelanotide had clinically meaningful and statistically significant improvements in their desire and associated distress which are the defining clinical issues for an HSDD diagnosis.

buprenorphine SL spray (Insys)

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

Route of Administration/Dosing: Sublingual therapy

Proposed Indication(s): Treatment of moderate-to-severe pain

Mechanism of Action: Partial mu-opioid agonist

Patient Impact: Millions of Americans suffer from acute or chronic pain every year. Generally, for acute pain this is often three days or less; more than seven days is rarely needed.

Comments: INSYS Therapeutics is developing buprenorphine sublingual spray for the management of moderate-to-severe acute pain. The company is using its proprietary spray technology to develop the sublingual formulation of buprenorphine. The company intends to seek approval of these products through the US FDA 505(b) (2) pathway. The NDA submission was supported by data from a study that met its primary efficacy endpoint in addition to several pharmacokinetic studies. Recently, the Company finished a 7-day safety and tolerability study among 100 patients for which the data will be submitted to the FDA in early 2018. Compared to other commonly used opioids, buprenorphine (as a partial mu-opioid agonist) offers a ceiling effect for respiratory depression and less abuse potential, less cognitive impairment, and less constipation. The company is using FDA's 505(b) (2) pathway to seek approval. The Prescription Drug User Fee Act (PDUFA) target date has been set for July 28, 2018 for completed NDA review.

PIPELINE REPORT

Brand Drug Detail - July 2018



cyclosporine A ophthalmic soln (OTX-101 - Sun)

Current Status: : This product is currently under FDA review with an action date of August 27, 2018

Route of Administration/Dosing: Ophthalmic therapy

Proposed Indication(s): Treatment of dry eye disease

Mechanism of Action: The exact mechanism of action is not known. Evidence indicates that inflammation of both the lacrimal gland and ocular surface is at the root of keratoconjunctivitis sicca, commonly referred to as dry eye disease. Topical cyclosporine may help to reduce that inflammation.

Patient Impact: Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. This in a market estimated to be worth more than \$2.4 billion, one that affects up to 100 million people worldwide, and one that is expected to grow by almost 3% yearly. The US dry eye target market is estimated at about 1.5-2 million patients.

Current Therapies: Restasis (cyclosporin ophthalmic emulsion 0.05% - Allergan); Xiidra (lifitegrast ophthalmic solution 5% - Shire)

Comments: OTX-101, a novel formulation of cyclosporine, is a clear, preservative-free, aqueous solution to help patients improve tear production coupled with a faster onset of action than Restasis. After 12 weeks of treatment, as compared to vehicle, OTX-101 showed statistically significant improvement in the primary end point, Schirmer's score (a measurement of tear production) ($p < 0.0001$). The demonstration of efficacy by OTX-101 at 12 weeks is earlier than other drugs approved for dry eye in the same class. Additionally, several key secondary endpoints showed statistically significant improvements compared to vehicle with some showing an even earlier onset of action. Adverse events reported in the trial were mild to moderate in nature and similar to other approved drugs in the category. As Sun continues to analyze the data, additional significant findings will be shared at upcoming medical conferences. Previously, in a completed Phase 2b/3 clinical trial in 455 patients, OTX-101 demonstrated a rapid onset of action and was well tolerated by the study population. Based on published data, the efficacy and safety endpoints in these trials compared favorably to other formulations of cyclosporine A with the advantage of faster onset. Dry Eye Disease, as defined by the National Health Institute (NHI), occurs when the eye does not produce tears properly, or when the tears are not of the correct consistency and evaporate too quickly. In addition, inflammation of the surface of the eye may occur along with dry eye. If left untreated, this condition can lead to pain, ulcers, or scars on the cornea, and some loss of vision. Dry eye can make it more difficult to perform some activities, such as using a computer or reading for an extended period of time, and it can decrease tolerance for dry environments, such as the air inside an airplane. Other names for dry eye include dry eye syndrome, keratoconjunctivitis sicca (KCS), dysfunctional tear syndrome, lacrimal keratoconjunctivitis, evaporative tear deficiency, aqueous tear deficiency, and LASIK-induced neurotrophic epitheliopathy (LNE).

dasotraline (Sunovion)

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

Route of Administration/Dosing: Oral therapy

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.

PIPELINE REPORT

Brand Drug Detail - July 2018



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 binge eating disorder (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 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 August 31, 2018.

elagolix (ABT-620 - AbbVie/Neurocrine)

Current Status: This product is currently under FDA review with an action date of August 06, 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

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 is a common disorder estimated to affect about one in 10 women in their reproductive years, or about 6.5 million women.

Comments: 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, progestins, danazol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and GnRH agonists, many of which are not specifically indicated for the treatment of endometriosis. Elagolix (ABT-620) is an oral gonadotropin-releasing hormone antagonist being studied for the treatment of endometriosis and uterine fibroid. On September 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. April 10, 2018: The PDUFA date was delayed with a new target date of July 27, 2018. Update: FDA requires more time to review the application, delaying the FDA action date by 3 months. The new estimated PDUFA date is August 6, 2018.

PIPELINE REPORT

Brand Drug Detail - July 2018



erenumab (Aimovig - Amgen/Novartis)

Current Status: BLA filed. FDA Approved: 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 FDA approved 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) - October 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.

estradiol softgel capsule (Yuvvey - TherapeuticsMD)

Current Status: This product is currently under FDA review with an action date of May 07, 2017

Route of Administration/Dosing: vaginal capsule (daily)

Proposed Indication(s): Applicator-free softgel capsule for the treatment of vulvar and vaginal atrophy in postmenopausal women.

Mechanism of Action: Bioidentical 17 β -estradiol

Patient Impact: It is estimated that over 33 million women in the U.S. suffer from vulvar and vaginal atrophy. About 7% are estimated to receive therapy for this condition.

Current Therapies: Premarin (conjugated estrogen - Pfizer), Estrace (estradiol vaginal cream - Allergan), Vagifem (estradiol vaginal inserts - Novo Nordisk)

PIPELINE REPORT

Brand Drug Detail - July 2018



Pipeline Product(s): Current leading products (Premarin, Estrace, Vagifem as well as others) have achieved total U.S. sales of roughly \$1.5B for the treatment of VVA (2016).

Comments: Yuvvexy (TX-004HR - TherapeuticsMD) is an investigational 17 β -estradiol vaginal drug product under FDA review for the treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women. It is an applicator-free VagiCap soft capsule technology that may prove to be easier to deliver than available product. Currently available products for the treatment of VVA are messy, inconvenient, and are generally disliked (creams and tablets). Despite some of the inconveniences and challenges to using these product, the current leading products (Premarin, Estrace, Vagifem as well as others) have achieved total U.S. sales of roughly \$1.5B for the treatment of VVA. Yuvvexy will compete for a portion of this market. The company had previously received a complete response letter for TX-004HR because its application lacked long-term safety data. The product was resubmitted (class 2, or 6 months review) with a new PDUFA date set for May 29, 2018.

fremanezumab (Teva)

Current Status: This product is currently under FDA review with an action date of June 16, 2018. Teva expects a complete response with approval by the end of 2018.

Route of Administration/Dosing: SC injection (225 mg once monthly or 675 mg quarterly); formulation may be too viscous to use an autoinjector which may require dosing in clinicians' offices.

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 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

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, Aimovig, 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.

galcanezumab (Lilly)

Current Status: This product is currently under FDA review with an action date of October 11, 2018

PIPELINE REPORT

Brand Drug Detail - July 2018



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

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 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): Teva’s TEV-48125, Eli Lilly’s LY2951742 and Amgen’s Aimovig (FDA approved May 17, 2018)

Comments: Migraine is a chronic, neurological condition associated with a moderate-to-severe throbbing headache often associated with symptoms that include nausea, vomiting, photophobia (sensitivity to light) and photophobia (sensitivity to sound). It affects approximately 12% of U.S. adults, or about 39 million Americans. Some patients suffer from frequent migraines and may be candidates for medications to prevent or reduce migraine frequency and severity. Calcitonin gene-related peptide, or CGRP, is believed to play an important role in the development of migraines. It is thought to be involved in several pathophysiological processes, including dilation of cerebral and dural blood vessels, release of inflammatory mediators from mast cells, and the transmission of pain information from intracranial blood vessels to the central nervous system. Therefore, blocking the effects of CGRP has become a target for development to treat migraines. While the place in therapy for the CGRP antagonists will continue to evolve, the initial therapies will be reserved for migraine prevention. Patients who do not adequately respond to, or cannot tolerate other preventive therapies may be candidates for the anti-CGRP therapies. Galcanezumab is a humanized monoclonal antibody that binds to and inhibits the effects of circulating CGRP. It is administered as a monthly subcutaneous injection for the prevention of migraines. In clinical trials (EVOLVE-1 and EVOLVE-2 Studies) patients with episodic migraine (<15 per month) treated with monthly doses of either galcanezumab 120mg or 240mg experienced a significantly greater decrease in the average number of monthly migraine headache days compared to patients treated with placebo (about a 2 day difference in the number of migraine days). The PDUFA date is set for October 11, 2018.

glycopyrronium tosylate (DRM04 - Dermira)

Current Status: This product is currently under FDA review with an action date of June 30, 2018

Route of Administration/Dosing: Topical therapy

Proposed Indication(s): Treatment of severe hyperhidrosis

Mechanism of Action: Glycopyrronium tosylate is a topical small-molecule anticholinergic product.

Patient Impact: Hyperhidrosis is a condition of excessive sweating beyond what is physiologically required to maintain normal thermal regulation. It can affect the axillae (underarms), palms of the hands, soles of the feet, face and other areas. In the United States, based on the most recent data available, the prevalence of hyperhidrosis was estimated in 2003 to be 2.8% of the population, or roughly 7.8 million people. According to published studies, approximately half of hyperhidrosis sufferers have axillary hyperhidrosis, and approximately one-third of axillary sufferers, or about 2.5 million Americans, have severe disease that is barely tolerable and frequently interferes or is intolerable and always interferes with daily activities.

PIPELINE REPORT

Brand Drug Detail - July 2018



Current Therapies: OTC products; Botox

Comments: Glycopyrronium tosylate is an investigational topical therapy for potential use in adult and adolescent patients who suffer from primary axillary hyperhidrosis (excessive underarm sweating), a medical condition that results in sweating beyond what is needed for normal body temperature regulation. If approved, glycopyrronium tosylate would be the first FDA-approved topical wipe medication specifically indicated to treat patients with primary axillary hyperhidrosis. Botox has already been used to treat hyperhidrosis and ~90%-95% of the patients were able to get their Botox treatment covered. Therefore, the pricing environment is relatively well-established with the payers. In addition to the treatment of axillary hyperhidrosis, the company has also highlighted a few potential ways to expand the market, including excessive sweating of the palm and feet, or even an over-the-counter (OTC) opportunity in the long term for heavy sweating. On February 17, 2018, Dermira presented new findings from its glycopyrronium tosylate Phase 3 clinical program showing that when applied topically, the investigational therapy improved disease severity, reduced sweat production and was associated with improved quality of life outcomes for pediatric patients (ages 9 to 16) with primary axillary hyperhidrosis, compared to vehicle-treated patients.

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 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 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.

insulin glargine (Semglee - Mylan/Biocon)

Current Status: This product is currently under FDA review with an action date in July 2018

Route of Administration/Dosing: Subcutaneous (SQ) therapy

Proposed Indication(s): A long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

PIPELINE REPORT

Brand Drug Detail - July 2018



Mechanism of Action: The primary activity of insulin is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

Patient Impact: If approved Basalog would provide patients with another form of once daily insulin analog. An estimated 22.5 million adults will be diagnosed with type 2 diabetes. In the US, basal insulin market is estimated at more than \$6 billion.

Comments: This product has similar efficacy and safety as Lantus in treatment of patients with type 1 diabetes mellitus. Mylan and Biocon, which are co-developed insulin glargine, is looking forward to offering another insulin treatment option for diabetic patients, who are often facing significant expense to manage their disease. This filing includes analytical, functional and pre-clinical data, as well as results from the pharmacokinetics (PK) and confirmatory efficacy/safety global clinical trial in Type 2 diabetes patients comparing Mylan's and Biocon's Insulin glargine with Lantus. The PK study demonstrated PK and PD bioequivalence of Mylan's and Biocon's insulin glargine relative to that of the reference drug Lantus. This product is currently under FDA review with an action date in July 2018.

lofexidine (Lucemyra - US WorldMeds)

Current Status: FDA Approved May 26, 2018

Route of Administration/Dosing: Oral therapy

Proposed Indication(s): To mitigate opioid withdrawal symptoms

Mechanism of Action: Selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine to reduce the severity of withdrawal symptoms in patients experiencing opioid withdrawal.

Patient Impact: Opioid use disorder is a medical condition characterized by a problematic pattern of opioid use that causes clinically significant impairment or distress. In the United States in 2015 there were 33,000 deaths due to drug overdose involving opioids. The prevalence of opioid use and opioid or opiate dependency varies by age and gender, among a wide variety of other factors. Men are at higher risk for opioid use and dependency than women, and men also account for more opioid overdoses than women, although this gap is closing. Women are more likely to be prescribed pain relievers, be given higher doses, use them for longer durations, and may become dependent upon them faster.

Comments: Lofexidine, an oral alpha-2 adrenergic receptor agonist, works by suppressing the neurochemical surge that produces the acute and painful symptoms of opioid withdrawal. Opioids lower norepinephrine, a brain chemical that supports vital functions like respiration and consciousness. With continued opioid use the brain establishes a new equilibrium by increasing compensatory norepinephrine production in order to maintain normal functioning. When opioids are removed, or the dose significantly reduced, the brain's increased norepinephrine levels are no longer offset by the presence of the opioids. This results in a norepinephrine surge that produces the acute and painful symptoms of withdrawal. The New Drug Application (NDA) for lofexidine contains data from 2 randomized, double-blind, placebo-controlled clinical trials and other supporting studies. In placebo-controlled trials, treatment with lofexidine resulted in less severe withdrawal symptoms and patients were more likely to finish opioid discontinuation treatment. In March 2018, a Food and Drug Administration (FDA) Psychopharmacologic Drugs Advisory Committee voted in favor (11 to 1) of recommending approval of lofexidine (Lucemyra) for the mitigation of opioid withdrawal symptoms. The FDA has set a target Prescription Drug User Fee Act (PDUFA) action date in the second quarter of 2018. FDA approved May 16, 2018.

oxycodone, extended-release (Remoxy - Pain Therapeutics)

Current Status: This product is currently under FDA review with an estimated action date of August 12, 2018

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

PIPELINE REPORT

Brand Drug Detail - July 2018



Proposed Indication(s): Twice-daily treatment of moderate to severe pain requiring continuous opioid use for an extended period of time.

Mechanism of Action: Abuse-deterrent opioid product containing the opioid analgesic, oxycodone

Patient Impact: Another treatment option for treating chronic pain. \$7 billion U.S. opioid market. Globally, the pain med market is \$50 billion.

Comments: Pfizer expects to meet the FDA in late March 2013 to discuss data from its ongoing confirmatory bioavailability study to assess the pharmacokinetic profile of modified REMOXY formulation compositions. Based on feedback Pfizer receives from the FDA at the meeting, Pfizer will subsequently determine the next steps and/or required timing to respond to the Complete Response Letter. Remoxy is intended to meet the needs of physicians who appropriately prescribe opioid painkillers and who seek to minimize risks of drug diversion, abuse or accidental patient misuse. Remoxy resists injection or snorting. Published data also show that freezing, crushing or submerging Remoxy in high-proof alcohol for hours at a time releases just a fraction of oxycodone at time points when abusers presumably expect to get high. 03/29/2016 The NDA for Remoxy was resubmitted with a priority review. FDA is expected to rule on the approval of Remoxy by Sep. 25, 2016. 07/05/2016 Update: An FDA Advisory Committee will meet to discuss this product on August 05, 2016. The PDUFA date (currently) remains unchanged at 09/25/2016. Complete Responses letter (CRL) received. UPDATE: 02/15/2018: Pain Therapeutics announced the resubmission of the New Drug Application (NDA) for Remoxy ER. The company expects a six month review cycle by FDA (Class 2 resubmission). An FDA Advisory Committee will meet to discuss this drug on June 26, 2018.

prucalopride (Resolor - Shire)

Current Status: This product is currently under FDA review with an action date of December 21, 2018

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

Proposed Indication(s): Prucalopride is being evaluated as a potential once-daily treatment option for chronic idiopathic constipation (CIC) in adults.

Mechanism of Action: Selective 5-HT₄ agonist

Patient Impact: Chronic idiopathic constipation affects an estimated 35 million people in the US.

Comments: Prucalopride (proposed brand name Resolor) is a drug acting as a selective, high affinity 5-HT₄ receptor agonist which targets the impaired motility associated with chronic constipation, thus normalizing bowel movements. It increases bowel motility by stimulating colonic peristalsis (wave-like movements that push contents forward). Prucalopride was approved for use in Europe in 2009 and in Canada on December 7, 2011 but it has not been approved by the Food and Drug Administration for use in the United States. Prucalopride has been studied in more than 90 clinical trials worldwide over the last 20 years, including five main Phase 3 and one Phase 4 double-blind, placebo-controlled clinical trials that informed the NDA submission. Due to the cardiac concerns with the 5-HT₄ agonists' cisapride, there were concerns about the risk of cardiac side effects of prucalopride. In clinical trials, there was no increased incidence of prolongation of the QT interval or bradycardia in the prucalopride group compared to placebo. Prucalopride seems to be effective for the management of chronic constipation resistant to conventional laxatives. This product is currently under FDA review with an action date of December 21, 2018.

sarecycline (Seysara - Allergan / Paratek)

Current Status: This product is currently under FDA review with an action date of October 20, 2018

Route of Administration/Dosing: Oral therapy (daily)

Proposed Indication(s): Treatment of moderate to severe acne vulgaris in patients 9 years of age and older.

PIPELINE REPORT

Brand Drug Detail - July 2018



Mechanism of Action: Sarecycline is a once-daily, oral, narrow-spectrum tetracycline.

Patient Impact: Moderate-to-severe acne affects around 20% of young people and severity correlates with pubertal maturity. Although acne is most common in adolescents, it can persist into the 20s and 30s in around 64% and 43% of individuals, respectively.

Current Therapies: There are several generically available tetracycline-derived antibiotics approved for treating acne vulgaris.

Comments: In October 2017, Allergan submitted a New Drug Application to the US Food and Drug Administration for sarecycline for the treatment of moderate to severe acne vulgaris in patients 9 years of age and older. In December 2017, the US FDA accepted the NDA for review. The application was based on results from two phase III trials [see below], which met their primary efficacy endpoints. The application includes two identically-designed, large, multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies, which demonstrated that once-daily sarecycline 1.5 mg/kg significantly improved acne severity based on Investigator's Global Assessment (IGA) success, and significantly reduced inflammatory lesion count vs placebo at week 12 in patients with moderate to severe facial acne vulgaris. In March 2017, Allergan announced positive results of these Phase 3 studies, which met their primary efficacy endpoints. The estimated PDUFA date is October 20, 2018.

sodium zirconium cyclosilicate (ZS9 - AstraZeneca)

Current Status: Complete Responses Letter issued

Route of Administration/Dosing: Oral therapy administered three times daily, with meals, for treating hyperkalemia. The dose can be changed to once daily for maintaining potassium levels.

Proposed Indication(s): Treatment of hyperkalemia

Mechanism of Action: It is a non-absorbed compound with a three dimensional crystalline lattice structure designed to specifically trap potassium ions.

Patient Impact: Potassium retention leading to increased serum potassium is common in patients with CHF and CKD due to impaired kidney function. Hyperkalemia may lead to arrhythmia and sudden cardiac death, therefore, management of hyperkalemia could decrease mortality and broaden current limitations of renin-angiotensin aldosterone system (ACE inhibitors, angiotensin II receptor antagonists, aldosterone antagonists) blockade treatment in patients with CHF and CKD. The U.S. market opportunity for Patiomer in hyperkalemia is large, with over 2 million moderate to severe hyperkalemia patients presenting to specialist physicians. In general, hyperkalemia frequency can be as high as 40-50% in the CKD population compared to 2-3% in the general population.

Current Therapies: Veltassa (patiomer - Relypsa) and Kayexalate (Sodium Polystyrene)

Comments: Sodium zirconium cyclosilicate (ZS-9) is an insoluble, non-absorbed zirconium silicate with a clearly defined three-dimensional crystalline lattice structure that was designed and engineered to preferentially trap potassium ions. The potassium selectivity of ZS-9 enables high in-vitro binding capacity for potassium ions even in the presence of other competing ions. It will compete for market share with Kayexalate (sodium polystyrene sulfonate) and recently approved Veltassa (patiomer -Relypsa). Veltassa is approved for treating hyperkalemia, not limited to renal failure or CHF. There also is not a limit to the duration of treatment. Veltassa, with its long onset of action, should also not be used for treating acute hyperkalemia. On the negative side, the product labeling indicated that other medications cannot be taken 6 hours before or after Veltassa. A similar change was made to the labeling for Kayexalate to reflect a similar possible drug interaction. ZS-9, on the other hand, could possibly be used for the acute and chronic maintenance treatment of hyperkalemia. Since the crystalline structure preferentially traps the potassium ion, it may not have a similar drug interaction as Veltassa and Kayexalate. AstraZeneca recently acquired ZS pharma for \$2.7 billion. This should be an indication of the potential market potential for the new products for treating hyperkalemia. Analysts estimate that these drugs could compete for market share in a potential \$1 billion market.

PIPELINE REPORT

Brand Drug Detail - July 2018



solriamfetol (JZP-110 - Jazz Pharmaceuticals)

Current Status: This product is currently under FDA review with an action date of December 20, 2018

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 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 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). Update: Jazz submitted the NDA for solriamfetol (JZP-110) on December 20, 2017 with a projected PDUFA date of December 20, 2018.

sotagliflozin (Lexicon / Sanofi)

Current Status: This product is currently under FDA review with an action date of March 16, 2019

Route of Administration/Dosing: Oral therapy

Proposed Indication(s): Use, in combination with insulin therapy, to improve glycemic control in adults with type 1 diabetes mellitus.

Mechanism of Action: LX4211 is an oral, first-in-class, dual inhibitor of sodium glucose transporters 1 and 2 (SGLT1 and SGLT2).

Patient Impact: It is estimated that 1.5 million Americans have type 1 diabetes. This product is also under investigation for treating type 2 diabetes (phase 3).

Comments: Sotagliflozin is a dual inhibitor of SGLT-1 and SGLT-2 to influence how the intestines and kidneys process blood sugar, respectively. Top-line results in a Phase 2 clinical trial of LX4211 in type 1 diabetes, which achieved the primary endpoint of reducing mealtime insulin use as well as several secondary endpoints, including improved glycemic control. LX4211 is an oral, first-in-class, dual inhibitor of sodium glucose transporters 1 and 2 (SGLT1 and SGLT2) that is designed to lower blood glucose levels through two insulin-independent mechanisms of action. The filing is based on data from the inTandem clinical trial program, which consists of three phase 3 clinical trials assessing the safety and efficacy of sotagliflozin in approximately 3,000 adults with inadequately-controlled type 1 diabetes. Some analysts estimate that sotagliflozin sales could reach \$1.2 billion by 2022.

PIPELINE REPORT

Brand Drug Detail - July 2018



ulipristal acetate (Esmya - Allergan)

Current Status: This product is currently under FDA review with approval expected in August 2018

Route of Administration/Dosing: Oral therapy (daily)

Proposed Indication(s): Progesterone agonist/antagonist for the treatment of abnormal uterine bleeding in women with uterine fibroids.

Mechanism of Action: The drug is a selective progesterone receptor modulator (SPRM), which acts directly on the progesterone receptors in three target tissues: the endometrium (uterine lining), uterine fibroids, and the pituitary gland.

Patient Impact: The patient population is sizable—an estimated 26 million American women between the ages of 15 and 50 years.

Comments: Currently, surgery is a common treatment option for symptomatic uterine fibroids. In fact, uterine fibroids are responsible for over 350,000 hospitalizations and are the leading cause of hysterectomies, accounting for more than one-third of all hysterectomies annually in the U.S. Ulipristal acetate is an investigational drug in the U.S. in development for the medical treatment of abnormal uterine bleeding in women with uterine fibroids. As Allergan seeks U.S. approval for Esmya, the E.U. is investigating the treatment for liver damage. The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has launched a review of the product after four cases of serious liver damage turned up among patients. Three of those cases ended in liver transplantation, the EMA noted. However, this is just something to watch. Allergan does not expect the investigation to have an impact on its New Drug Application in the U.S. as no cases of liver transplantation came up in any of the controlled clinical trials for Esmya in the EU, Canada or the U.S. Due to the size of the market, this product is a potential blockbuster medication.