

Orphan Diseases:
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Alzheimer's Disease:
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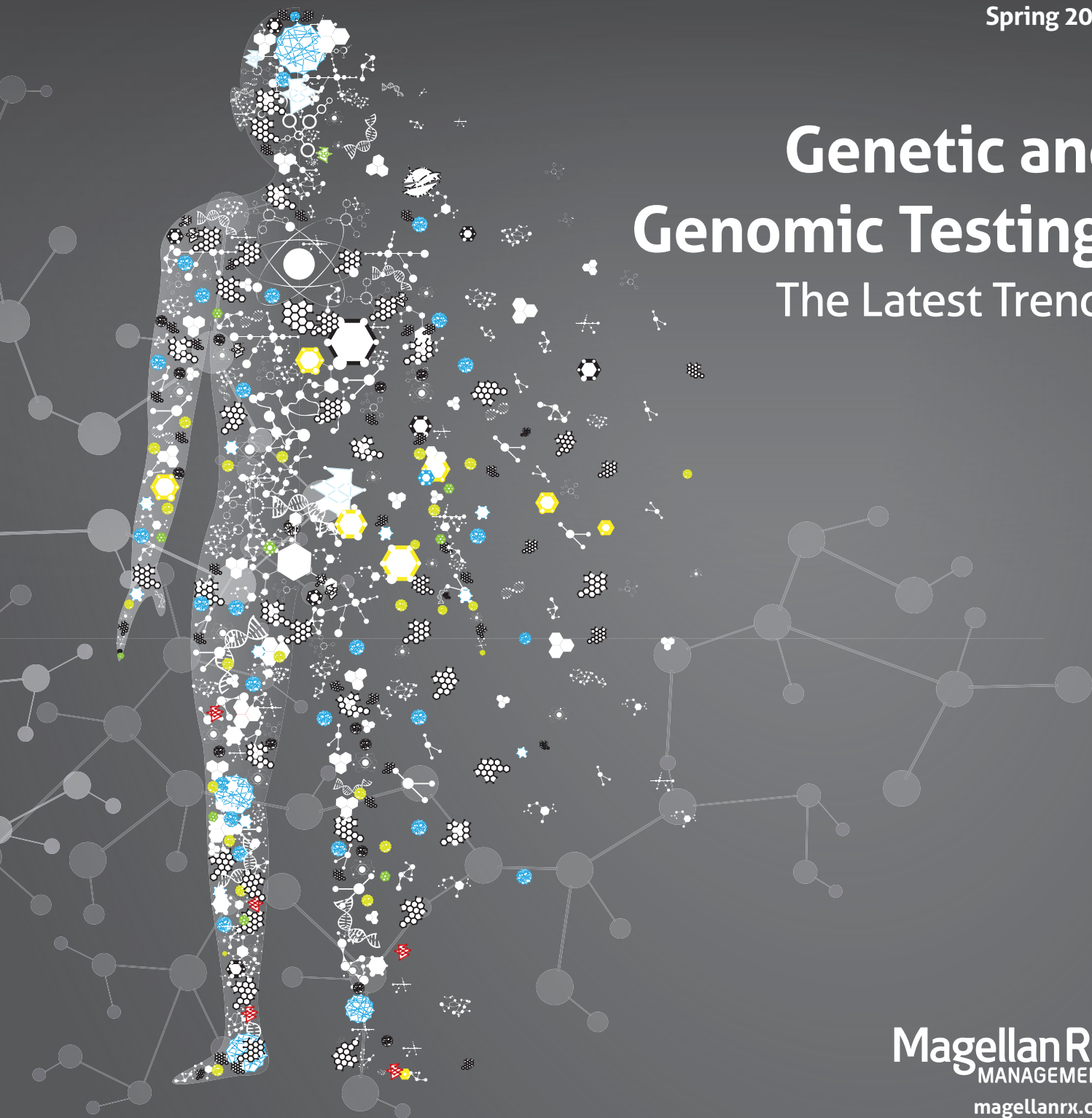
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and Treatment
Landscape Update

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Spring 2018

Genetic and Genomic Testing: The Latest Trends



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HOW CAN YOU HELP PROTECT PATIENTS AGAINST LOSS OF VISION?

Your members with retinal diseases* may be facing the serious risk of vision loss without screening and doctor-recommended treatment.¹⁻³ Vision loss may require ongoing resources.¹⁻³

THERE'S EYLEA—a treatment option that can fit your plans for proven visual acuity outcomes

- ✓ EYLEA has proven outcomes as demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in patients with DME
- ✓ With monthly and every-other-month dosing,[†] EYLEA offers flexible dosing options to meet the needs of your providers and your members

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

- EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

*The FDA-approved indications for EYLEA are Wet AMD, Macular Edema following RVO, DME, and DR in Patients with DME.

[†]After an initial monthly dosing period for certain indications.

References: 1. American Academy of Ophthalmology. Preferred Practice Pattern®: Age-Related Macular Degeneration. <http://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp-2015>. 2. American Academy of Ophthalmology. Preferred Practice Pattern®: Retinal Vein Occlusions. <http://www.aao.org/preferred-practice-pattern/retinal-vein-occlusions-ppp-2015>. 3. American Academy of Ophthalmology. Preferred Practice Pattern®: Diabetic Retinopathy. <http://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp-updated-2016>.

Please see brief summary of full Prescribing Information on the following page.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON

- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

 **EYLEA®**
(aflibercept) Injection
For Intravitreal Injection

EYLEA® (afibercept) Injection For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.

1 INDICATIONS AND USAGE

EYLEA® (afibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection, EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR) in Patients with DME. The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x 1/2-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

2.7 Injection Procedure. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad-spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (see *Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periorbital infections
 - Active intraocular inflammation
 - Known hypersensitivity to afibercept or any of the excipients in EYLEA.
- Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (see *Adverse Reactions*). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (see *Dosage and Administration* and *Patient Counseling Information*).

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (see *Adverse Reactions*). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (see *Dosage and Administration*).

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

6.1 Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice. A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

6.3 Postmarketing Experience. The following adverse reactions have been identified during postapproval use of EYLEA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity including rash, pruritus, and urticaria as well as isolated cases of severe anaphylactic/anaphylactoid reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Afibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternbrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal NO Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Afibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

8.3 Nursing Mothers. It is unknown whether afibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (see *Warnings and Precautions*). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (see *Adverse Reactions*). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

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**2017 Medical
Pharmacy Trend
Report: Key Findings**



Mostafa Kamal
Chief Executive Officer
Magellan Rx Management

Dear Managed Care Colleagues,

Welcome to our spring issue of the Magellan Rx™ Report! In 2017, there were many exciting changes taking place at the Food and Drug Administration (FDA). Last year, there were 46 novel drug approvals, which more than doubled the number of approvals

in 2016. We also experienced a momentous event when the FDA approved the first gene therapy in the U.S. This therapy was approved for the treatment of a rare form of childhood blindness for which treatment previously did not exist. We also saw improvements in median drug review times, dropping from eleven months between 2015 and 2016 to eight months in 2017.

Many of these therapies are highlighted in one of our feature articles, which reviews newly approved therapeutic advances in the treatment of rare diseases, including the first gene therapy mentioned previously. The piece also lists investigational agents currently being studied for the treatment of rare diseases.

Another feature article examines the differences between genetic and genomic testing. Over the last few years, pharmaceutical companies' research and development efforts have shifted toward the expansion of the availability of precision medicine — diagnostics and interventions tailored to the individual patient's genomics. The availability of personalized medicine brings new challenges, including a rise in interest among patients to have genomic testing performed

and coverage determinations for companion diagnostics and treatments. This article reviews the managed care implications of notable trends in the future of medicine.

Other notable topics discussed in this issue include a spotlight on the benefit of utilizing key opinion leader services, including peer-to-peer discussions and second opinions; investigational agents for the treatment of Alzheimer's disease; legislative updates for opioids and substance use disorder treatment; an update on the treatment pipeline for migraine and uterine fibroids; and a retrospective analysis of health resource utilization among Medicaid superutilizers with schizophrenia.

No issue of the Report would be complete without a pharmaceutical pipeline review to help you track promising new agents that may receive FDA approval in the near future.

To learn more about Magellan Rx Management and our support of payor initiatives of the future, please feel free to contact us at MagellanRxReport@magellanhealth.com. As always, I value any feedback that you may have, and thanks for reading!

Sincerely,

Mostafa Kamal
Chief Executive Officer
Magellan Rx Management

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Managed Care Newsstand

Mostafa Kamal Named to the Substance Use Disorder Treatment Task Force Founded by Shatterproof

In November 2017, Mostafa Kamal, CEO of Magellan Rx Management, was named to Shatterproof's Substance Use Disorder Treatment Task Force. The mission of the task force, which launched in April 2017, is to "fundamentally improve substance use disorder [SUD] treatment in the United States, in terms of both quality and patient outcomes." As part of the task force, payors, including Magellan Health, announced a

groundbreaking commitment to adopt eight National Principles of Care for the treatment of addiction that will improve outcomes and save lives. The organizations agreed to identify, promote, and reward substance use disorder treatment that aligns with the National Principles of Care, which were derived from the Surgeon General's Report on Alcohol, Drugs, and Health. Aligning care with these evidence-based principles will significantly improve the quality of treatment for the millions of Americans with substance use disorders.

"I am honored to serve as a member of this task force and to be joining other colleagues and experts from across the

industry to address the lack of quality treatment for the estimated 21 million Americans with substance use disorders," Kamal says. "The work of this task force aligns well with Magellan's solution as we help individuals contending with SUD from both the behavioral health and the pharmacy perspective."

Source: Magellan Rx Management CEO Mostafa Kamal named to Shatterproof's Substance Use Disorder Treatment Task Force. Press release. Scottsdale, AZ: Magellan Health Inc. 2017 Nov 9. <http://ir.magellanhealth.com/releasedetail.cfm?ReleaseID=1048128>. Accessed 2018 Jan 30.

DEA Deregulatory Measure Expands Number of Healthcare Professionals with Buprenorphine Prescribing Authority

In January 2018, the U.S. Drug Enforcement Administration (DEA) announced a deregulatory measure that would allow nurse practitioners and physician assistants to become Drug Addiction Treatment Act (DATA)-Waived qualifying practitioners, thereby giving them the authority to prescribe and dispense the opioid-maintenance drug buprenorphine from their offices. This measure aims to make it easier for residents of underserved areas to receive treatment for opioid addiction.

Before the enactment of DATA in 2000, only physicians were permitted to treat those with opioid addiction, and these physicians were required to register with the DEA as both physicians and operators of narcotic treatment programs. Through the waiving of the second registration as operators of narcotic treatment programs, more physicians were able to offer treatment services.

In 2016, the Comprehensive Addiction



90% of DATA-Waived physicians were practicing in urban counties

of rural counties had no prescribing physician available



and Recovery Act (CARA) was passed by Congress and signed into law. At that time, the DEA began to transition mid-level practitioners into DATA-Waived status to increase the number of providers who could treat individuals with drug addiction.

Prior to the enactment of CARA, the majority of DATA-Waived physicians served urban areas, and rural regions of the U.S. were underserved. In a 2017 National Rural Health Association report, 90% of DATA-Waived physicians were practicing in urban counties, with 53%

of rural counties having no prescribing physician available and 30 million people living in counties where treatment was unavailable. Therefore, rural patients seeking outpatient buprenorphine treatment were required to travel long distances to access care. Furthermore, rural providers reported a demand that exceeded their capacity and a lack of resources needed to offer adequate support. The report also found that 92% of substance use treatment facilities were located in urban areas, and rural areas offered fewer inpatient and day treatment resources.

Currently, there are approximately 43,000 DATA-Waived qualifying providers in the U.S., with about 5,000 mid-level practitioners able to treat and prescribe for patients with opioid addiction. This measure offers more treatment options to patients with addiction in these previously underserved areas and brings DEA regulations into conformity with CARA.

Source: DEA announces step to increase opioid addiction treatment. Washington, D.C.: DEA Public Affairs. Press release. 2018 Jan 23. <http://www.dea.gov/divisions/hq/2018/hq012318.shtml>. Accessed 2018 Jan 30.

Magellan Launches New Digital Tool for Pain Management

Magellan Health is a recognized leading provider of digital tools to increase the integration of and access to medical and behavioral health treatment. One part of Magellan's broad-based digital strategy is the Virtual Care Solution (VCS), an innovative platform and portal, which includes a collection of digital and digitally enabled telehealth programs that help identify and support those with medical and behavioral health conditions. Magellan's software suite includes apps for the following:

- mood (MoodCalmer)
- anxiety, panic, and phobia (FearFighter™)
- sleep difficulty and insomnia (Restore™)

Magellan's software also includes web-based modules for the following:

- substance and alcohol misuse (Shade)
- obsessive-compulsive disorder (OCFighter)

Recently, Magellan announced the launch of the newest addition to its suite of digital cognitive behavioral therapy (DCBT) programs: ComfortAble™.

Designed for those impacted by chronic pain, the module aims to help users reduce pain or see significant improvements in functioning. The module uses proven cognitive behavioral therapy techniques to help users identify and change unhelpful thinking and behavior patterns and learn new problem-solving techniques. ComfortAble™ features the following:

- clinical vignettes
- interactive multimedia activities
- exercises that facilitate the development of new skills

Users can track their progress through each session. Upon completion, new resources and activities are assigned.

The VCS platform enhances the delivery of services to underserved areas and to individuals who may find it challenging to find time to see a provider in person. The modules are available in both English and Spanish, are designed to be culturally sensitive, support a range of literacy needs, and can be accessed on most mobile devices. At any given time, more than 2,000 people are actively using Magellan's VCS and engaging in these digital programs.

ComfortAble™ is offered as a smartphone app for members of Magellan client health plans. These modules are available on the Apple App Store and

Google Play. Magellan is also developing a new module focused on opioid addiction.

Seth Feuerstein, MD, JD, chief innovation officer for Magellan Health says, "With the launch of ComfortAble™, Magellan maintains our market differentiation as the only organization to offer the most robust suite of DCBT programs that expands access to evidence-based care, addresses complex conditions, and improves the health of our members. By taking a digital approach to CBT, as one aspect of our broader digital strategy, and using the power of data to drive innovation and continual program improvements, we are able to integrate into settings where individuals are already receiving medical care, such as federally qualified health centers, and also help people at any time and place that works for them."

Magellan's DCBT modules address the needs of those with complex conditions and have undergone numerous clinical trials in which they have matched, and in some instances exceeded, the outcomes reached by conventionally delivered CBT.

Source: Magellan expands digital innovation platform and strategy. Scottsdale, AZ: Magellan Health Inc. Press release. 2018 Mar 9. <http://ir.magellanhealth.com/news-releases/news-release-details/magellan-expands-digital-innovation-platform-and-strategy>. Accessed 2018 Mar 16.

Cost of U.S. Opioid Crisis Exceeds \$1 Trillion

A recent Altarum analysis revealed that the estimated cost of the opioid crisis in the U.S. exceeded \$1 trillion from 2001 to 2017. During this time period, the cost of the opioid crisis increased from \$29.1 billion annually to \$115 billion annually. Of note, between 2011 and 2016, the growth rate doubled compared to 2006 to 2011. Using these data, Altarum estimates that the cost of the opioid crisis, including the

cost of opioid misuse, substance use disorders, and premature mortality, will result in an additional \$500 billion by 2020, assuming current conditions persist.

From 2001 to 2017, opioid crisis-related healthcare costs reached almost \$216 billion, primarily due to emergency room visits, ambulance and naloxone-related costs, and indirect healthcare costs associated with the increased risk of other diseases or complications. Recently, Medicaid has taken on a disproportionately large share of this cost. Analysts have suggested that policymakers should

focus on prevention, treatment, and recovery to address the economic and human toll of the opioid crisis.

Source: Economic toll of opioid crisis in U.S. exceeded \$1 trillion since 2001. Washington, D.C.: Altarum. Press release. 2018 Feb 13. <http://altarum.org/about/news-and-events/economic-toll-of-opioid-crisis-in-u-s-exceeded-1-trillion-since-2001>. Accessed 2018 Feb 16.

Genetic and Genomic Testing:

A Q&A on the Differences, Clinical Applications, and Implications for Managed Care

What are the differences between genetic and genomic testing?

Evaluation of the human genome is becoming increasingly important as medical breakthroughs allow for more tailored, personalized approaches to treatment. It is estimated that genetic defects or mutations are responsible for more than 35% of pediatric medical conditions. For adults, the cause of disease is frequently multifactorial, with both genetic and environmental influences playing a role.¹



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Genetic and genomic testing are commonly confused, and the terms are often incorrectly used interchangeably, as both techniques examine the composition of an individual's deoxyribonucleic acid (DNA). The key difference between these two methods is that genetic testing is used to identify abnormalities in the DNA that are inherited from the individual's parents, while genomic testing is used to detect abnormalities in the DNA that have been acquired over time. Genetic testing focuses on a specific gene, while genomic testing evaluates a larger section of the DNA sequence.^{1,2}

How have genetic and genomic testing been used?

Genetic testing may be used to determine the presence of genetic disease or to predict an individual's risk of ultimately developing a genetic disease. Genomic testing, on the other hand, may be used to characterize a disease that an individual has already developed. For example, genetic testing is commonly used to diagnose inherited diseases such as cystic fibrosis, trisomy 21 (Down syndrome), hemophilia, Huntington's disease, phenylketonuria (PKU), and sickle cell disease.³ Genomic testing is often used in oncology and may be used to detect acquired genetic abnormalities that are responsible for the majority of cancers and may influence the growth and spread of a tumor. The results of genomic testing can then be used to predict the individual's likely response to certain therapies so that an individualized treatment plan can be developed accordingly. In addition to oncology, other diseases that have been studied in the emerging field of genomics include asthma, diabetes, and heart disease. These disease states are ideal candidates for further research because they are all associated with a combination of genetic and environmental factors rather than a single genetic defect.^{1,4}



Genetic testing has broad clinical applications and has had a significant impact on the way that genetic disease is diagnosed and treated. According to the National Institutes of Health, research laboratories are now capable of conducting genetic testing for 2,000 or more rare and common hereditary conditions.^{3,5} In the U.S., infants are screened shortly after birth to identify genetic disorders that may be treated early in life. For example, all 50 states currently test newborns for PKU and congenital hypothyroidism. If left untreated, these diseases may have significant consequences, but health outcomes may be dramatically improved if affected individuals are identified and treated early on.⁵

Several tests can provide important clinical information prior to pregnancy. Carrier testing is commonly conducted for two individuals who are planning to start a family. This type of testing can be used to detect copies of a gene mutation that may cause a genetic disorder when two copies are present (i.e., when both parents are carriers). This type of testing is often done for individuals with a known family history of genetic disease and those with an increased risk of specific conditions based on their ethnicity. The informa-

tion can then be used to determine a couple's risk of having a baby with a genetic disorder.³

Prenatal testing is a type of genetic test that is done after pregnancy begins. It is commonly used to detect or evaluate the risk of genetic mutations in a fetus prior to birth. While currently available prenatal screens are not able to detect all possible genetic disorders, the information garnered from this test can help couples make decisions about their pregnancy.³

Preimplantation testing is an important tool used to reduce the risk of genetic disease in infants who are born using assisted reproductive techniques (e.g. in vitro fertilization). Preimplantation testing detects genetic changes that may occur in embryos created via assisted reproductive techniques so that only embryos without these changes are implanted into the uterus to initiate pregnancy.³

Predictive testing is a valuable tool in determining an individual's risk of developing disease and informing healthcare decisions based on that risk. For example, if predictive testing detects an increased risk for an aggressive form of breast cancer, the individual and their healthcare provider may proactively employ more aggressive

preventive strategies, such as mastectomy, in an effort to improve long-term patient outcomes.³

As mentioned previously, genomic testing is most commonly used to characterize or diagnose a disease that is already present in an individual. Research suggests that genomic testing may yield important information that is key to improving patient outcomes. One study conducted at Rady Children's Institute for Genomic Medicine in San Diego enrolled 98 neonatal intensive care unit (NICU) patients.⁶ Within the first 48 to 72 hours of admission, blood samples were drawn and rapid whole genomic sequencing was completed within three to seven days. The investigators then translated the phenotypic features of each infant and mapped them to the genetic diseases with which they may be associated. Of the 98 study subjects enrolled, 34 (35%) received a genetic diagnosis following rapid whole genomic sequencing and 28 (80%) of those infants had changes in their medical management as a result. The investigators reported that some examples of changes in medical management included changes in medications, avoidance of unnecessary surgical procedures, and the determination that palliative care should be discussed with and considered by the family. In addition to the improvements observed in the medical management of the study participants, the investigators estimated that use of rapid whole genomic sequencing in this setting was associated with a net cost avoidance of \$1.3 million compared to the standard of care that would have otherwise been given.⁶

What techniques have been used in genetic and genomic testing?

There are several techniques used in genetic testing, and they range from evaluation of a single gene to evaluation of the entire genome.¹ Single gene analysis is used, as the name suggests, to analyze a single gene and may detect point mutations, nonsense mutations, frameshift mutations, de-

TABLE 1. DISEASE STATES AND DRUGS WITH COMPANION DIAGNOSTICS — SNAPSHOT

Disease State	Drug(s)
Breast cancer	Herceptin (trastuzumab)
	Kadcyla (ado-trastuzumab-emtansine)
	Perjeta (pertuzumab)
CML	Tasigna (nilotinib)
CRC	Erbitux (cetuximab)
NSCLC	Vectibix (panitumumab)
	Alecensa (alectinib)
	Gilotrif (afatinib)
	Iressa (gefitinib)
	Keytruda (pembrolizumab)
	Tafinlar (dabrafenib) + Mekinist (trametinib)
	Tagrisso (osimertinib)
	Tarceva (erlotinib)
	Xalkori (crizotinib)
	Zykadia (ceritinib)
Ovarian cancer	Lynparza (olaparib)
	Rubraca (rucaparib)

Abbreviations: CML = chronic myelogenous leukemia; CRC = colorectal cancer; NSCLC = non-small cell lung cancer

**Note: This table is not all-inclusive and does not include other disease states for which companion diagnostics exist (e.g. melanoma, chronic lymphocytic leukemia, etc.). It also does not include information regarding which biomarkers are tested. Please refer to the Food and Drug Administration's website for the most comprehensive and up-to-date information regarding cleared or approved companion diagnostic devices.*

letions, or insertions that are present within the coding region of the gene. This technique can be used to analyze a single genetic mutation, a panel of potentially pathogenic mutations, or the entire coding region of the gene. Selection of an appropriate target for the analysis is based on whether the specific mutation is already known (e.g. factor V Leiden mutation), whether a possible mutation needs to be

identified (e.g. possible mutations in the cystic fibrosis transmembrane conductance regulator [CFTR] gene), or whether there is a range of clinically significant mutations that may be spread across the entire gene (e.g. mutations in the gene for coagulation factor IX in hemophilia B).¹

Genotyping is used to characterize the combination of alleles to determine whether the individual is het-

erozygous (i.e., mutation affecting one allele), homozygous (i.e., mutation affecting both alleles), or compound heterozygous (i.e., two different mutations affecting each allele) for variants that may put the individual at greater risk for disease.¹

Gene panels may be used to analyze more than one gene for possible alterations associated with specific diseases. They may be indicated when there is a suspicion that an individual's disease may have genetic etiology. This specific type of genetic testing has been used to detect genetic associations for cardiomyopathy, metabolic disorders (e.g. hypercholesterolemia), cancer, and neurodevelopmental abnormalities. Similar to genomic testing, gene panels have the potential to identify unexpected mutations or mutations that the investigator was not specifically looking for.¹

In addition to various tests that work at the gene level, there are also several techniques that can be used to detect genetic variations at the level of copy number variants or the entire chromosome or chromosome segment. Such techniques include microarrays, fluorescence in situ hybridization (FISH), and high-resolution chromosome analysis. These tests have been used for the prenatal diagnosis of aneuploidies, characterization of hematologic malignancies, and analysis of previously unexplained congenital abnormalities in children.¹

Genomic testing requires advanced sequencing techniques that have collectively been referred to as next-generation sequencing. Using this approach, sequence information for the entire genome is elucidated, and unexpected mutations may be identified. In addition to identifying disease-causing mutations, critical information may be uncovered regarding carrier status, genetic predisposition for disease, and potential pharmacogenomic interactions.¹

Some examples of techniques currently being used in genomic testing include proteomics, or the analysis of all proteins in an organism, cell, or type of

tissue; and pharmacogenomics, which combines pharmacology with the study of genetic variables that may influence how individuals respond to certain drugs.^{1,4} Due to the large number of manufacturers, various genetic tests available, nuances surrounding which biomarkers can be tested using each test, and the differences in regulatory approval among these tests, the most up-to-date list of manufacturers and tests is constantly changing. As such, this article will not include a list of all tests and manufacturers, but rather a snapshot of select disease states that have companion diagnostics and accompanying drugs at the time of publication (see Table 1).

What clinical applications of genetic and genomic testing are currently being investigated?

Perhaps one of the most valuable uses of genetic and genomic testing is predicting how a patient may respond to a drug based on his or her individual characteristics. Adverse drug reactions may be associated with significant morbidity and mortality; and in the U.S. alone, such reactions are estimated to cause more than 100,000 deaths per year.⁷ Adverse drug reactions can be categorized as type A or type B reactions. Type A reactions are the most common (80% to 95% of all reactions) and are predictable based on our understanding of the drug's pharmacology. Type B reactions are rare but may be more severe and associated with morbidity and mortality. Unlike type A, type B reactions often have an unknown etiology, making them difficult to predict and prevent.⁷ Given the poor clinical outcomes and high medical costs associated with type B adverse drug reactions, there is significant interest in better understanding the role that genetics may play.^{7,8}

Pharmacogenomics is the study of how variations in genetic composition may affect an individual's response to drugs. Although pharmacogenetics — a phrase often used interchangeably with pharmacogenomics — was first

The ability to predict a patient's response to therapy may help optimize the selection of the drug, dose, and treatment duration indicated for a specific patient and may help prevent adverse drug reactions.

introduced in the 1950s, there has been increased interest in the field since 2003, following the completion of the Human Genome Project, which successfully sequenced the human genome.⁹ As our understanding of the role that genetics play in determining how an individual will respond to a drug increases, so does our ability to optimize drug therapy, mitigate the risk of adverse reactions, and improve overall patient outcomes. As more information has become available, the Food and Drug Administration (FDA) has updated the labeling for more than 200 approved drugs to include information about relevant genomic biomarkers.¹⁰ The additional information may describe the variability in drug exposure and/or clinical response, risk for adverse events, dosing based on specific genotype, mechanisms of action, and genetic polymorphisms in drug targets and disposition. Many of the biomarkers listed in the FDA's Table of Pharmacogenomic Biomarkers in Drug Labeling are metabolic biomarkers. Among those drugs listed, many are metabolized by enzymes in the cytochrome P450 (CYP) family. For example, drugs metabolized via the CYP2D6 pathway may have rates of metabolism that vary 100-fold or more based on the allelic variability that occurs among different ethnic groups.^{8,10} Approximately 7% of individuals of Western European descent are poor CYP2D6 metabolizers and require lower doses. Conversely, approximately 20 million individuals are ultra-rapid metabolizers who tend to have little or no response to standard doses.⁸

Several pharmacogenomic tests have been developed to detect the well-defined genetic variations that are known to have significant clinical consequences.⁸ Based on the test results, there may be clinical guidelines for adjustment of drug dose or for the selection of alternative drugs that have been established by the Clinical Pharmacogenetics Implementation Consortium. For example, if an individual is found to be a poor CYP2D6 metabolizer, the dose of doxepin should be reduced by 60% to avoid the potential side effects of arrhythmia and myelosuppression. Conversely, if the individual is an ultra-rapid CYP2D6 metabolizer, treatment with codeine should be avoided due to the potential for toxicity.⁸

While there has been considerable research and progress in identifying the genetic variants that influence drug metabolism, the development of genetic biomarker tests with the sensitivity, specificity, and predictive value to be useful in predicting drug efficacy and preventing adverse drug reactions has been less successful. The pharmacogenomic study of drug efficacy for common diseases can be challenging for multiple reasons, including that the clinical course of common disease is often influenced by both genetic and environmental factors. In addition, for many common diseases, not all of the genetic determinants that affect disease pathogenesis may be known. As a result, a drug may be ineffective because it is not targeting the appropriate factor or pathway.^{1,8} Drug efficacy and the course of disease may also be

influenced by the individual's medication regimen, diet, or a multitude of other environmental factors, making it challenging to control pharmacogenomic studies. To better understand the true clinical potential of pharmacogenomics, further genome-wide association studies, as well as data from next-generation sequencing, epigenetics, proteomics, and metabolomics are needed to identify functional genetic variants associated with drug efficacy and disease.⁸

What are the implications of genetic and genomic testing for managed care?

In addition to the diagnostic capabilities of genetic and genomic testing, advances in pharmacogenetic tests allow for the use of specific biomarkers to assess the probability of a positive response to a potential treatment. The ability to predict a patient's response to therapy may help optimize the selection of the drug, dose, and treatment duration indicated for a specific patient and may help prevent adverse drug reactions.^{1,3,11}

There are genetic tests currently available that can identify genetic mutations or deletions in order to predict health outcomes.¹² For example, it has been demonstrated that mutations on the epidermal growth factor receptor (EGFR), Kirsten ras (KRAS), and breast cancer susceptibility gene I and II (BRCA1 and BRCA2) are predictive of treatment resistance. Based on current understanding of these underlying mechanisms of resistance, new therapeutic classes have emerged specifically targeting these mutations. For patients with non-small cell lung cancer and EGFR mutations, a positive therapeutic response may be achieved by using tyrosine kinase inhibitors that target EGFR.¹² As the use of targeted therapies continues to increase, it is important for payors to consider strategies for ensuring appropriate use of targeted therapies, such as prior authorization programs requiring the use of the corresponding FDA-approved genetic tests. Given the increasing

cost associated with targeted therapies, it is imperative that payors support appropriate patient selection for these treatments.

With the increasing use of pharmacogenomics, perhaps the greatest challenge for payors is assessing the economic value that it provides.^{11,12} There is currently some published literature evaluating the value of genetic testing. Several literature reviews have found that economic analyses of genetic tests have had flaws that may affect the applicability of the data, such

as poor reporting of the influence of potential bias on the cost-effectiveness estimates. In general, evidence reviews have found genetic testing to be cost-effective or even cost-saving in some situations; however, more data is needed to gain a better understanding of the value provided. Payors should continue to analyze new data as it becomes available and adjust their management strategies accordingly.¹²

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Orphan Diseases:

Highlighting Product Developments for the Treatment of Rare Diseases

The Orphan Drug Act of 1983 defines an orphan disease as being a rare disease that affects fewer than 200,000 individuals in the U.S. Nearly 7,000 disease states qualify under the legislation, affecting approximately 30 million individuals.¹ The vast majority of rare diseases, about 80%, are genetic in nature and most lack effective treatment options.^{1,2}



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In an effort to promote the development of products for the diagnosis and/or treatment of rare diseases, the Food and Drug Administration's (FDA) Office of Orphan Products Development administers an Orphan Drug Designation program.³ The purpose of this program is to incentivize drug manufacturers to invest in the research and development of products that may ultimately diagnose, treat, or prevent rare diseases. Previously, drug manufacturers were awarded a 50% tax credit for clinical research expenses, a waiver of the user fees associated with the Prescription Drug User Fee Act, and seven years of marketing exclusivity for the product or new indication following approval. As of 2018, the tax credit for clinical research expenses was reduced to 25% after a bill was passed by Congress in December 2017.

Since the inception of the Orphan Drug Act, more than 600 small molecules and biologics for the treatment

of rare diseases have come to market.⁴ Between 2010 and 2015, approximately one-third of all new drug approvals were for rare diseases.⁵ Additionally, from 2013 to 2017, the FDA approved 91 novel drugs and 88 new indications for products that were considered orphan drugs; yet it is estimated that only 5% of rare diseases have FDA-approved treatments available.³ Considering the aforementioned incentives and the high costs that drug manufacturers may charge for their products, the development of orphan drugs has become a highly lucrative opportunity.^{3,6} More than 500 agents to target rare diseases are in development.

Innovation

Perhaps the greatest contributor to recent breakthroughs in rare disease drug development has been the completion of the National Human Genome Project in 2003. Initiated in 1990, the Human Genome Project was a joint effort by the Human Genome Research Institute (NHGRI) and the Department of Energy (DOE), to sequence all 3 billion letters in the human genome. The purpose of this work was to provide researchers with insight into the role that genetics plays in human disease, ultimately yielding new strategies for the diagnosis, treatment, and prevention of various diseases.⁷ Advancements in technology, coupled with a greater understanding of the human genome, have enabled

From 2013 to 2017, the FDA approved 91 novel drugs and 88 new indications for products that were considered orphan drugs; yet it is estimated that only 5% of rare diseases have FDA-approved treatments available.

researchers to target specific genetic mutations with precision, leading to truly personalized medicine. According to a report from the National Institutes of Health (NIH), the Human Genome Project has led to the discovery of more than 1,800 disease genes and the development of more than 2,000 genetic tests for human disease.⁷

With thousands of agents in development for rare diseases, it is not possible to include all investigational agents in this review; however, Table 1 contains a snapshot of late-stage investigational agents for rare diseases. The primary areas of innovation that will be discussed in this article include gene therapy using the adeno-associated virus (AAV), gene silencing with ribonucleic acid interference (RNAi) technology, and genome editing using clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated (Cas) genes. These areas of innovation are among the most cutting-edge technologies in use for the treatment of rare diseases.

Gene Therapy: Use of AAV

Gene therapy uses genetic material to manipulate a patient's cells to treat an inherited or acquired disease.⁸ Genetic material (e.g. nucleic acids, viruses, or genetically engineered microorganisms) that is inserted directly into the cell is typically not functional and requires a genetically engineered vector to deliver the gene.⁹ Viruses serve as some of the most efficient vectors; modified viruses can insert genetic material into the cell by infecting the cell, but the modifications prevent that virus from causing disease in the human host.¹⁰ Commonly utilized viruses include retroviruses and

adenoviruses; retroviruses are able to integrate their genetic material into a chromosome in the human cell, while adenoviruses introduce deoxyribonucleic acid (DNA) into the nucleus of the cell but not into the chromosome.¹¹

VORETIGENE NEPARVOVEC

In late 2017, the FDA approved the first gene therapy, Luxturna (voretigene neparvec), for the treatment of RPE65 mutation-associated retinal dystrophy.¹² Voretigene neparvec uses an AAV to insert a normal copy of the RPE65 gene directly into retinal cells. With the introduction of a normal copy of the gene, the retinal cells are then able to produce the normal protein that converts light to an electrical signal in the retina, potentially restoring lost vision.¹² Treatment with voretigene neparvec was studied in a pivotal phase III clinical trial (N=31). The most common adverse reactions in clinical trials were ocular in nature, some of which included conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, macular hole, subretinal deposits, and maculopathy, among others.¹³ One year after treatment, study subjects completed the multi-luminance mobility test (MLMT), and patients in the intervention group had greater mean bilateral MLMT change scores compared to patients in the control group. The change in MLMT that may be achieved with voretigene neparvec may result in improvements in functional vision, allowing individuals who suffer from blindness to complete basic but essential activities of daily living independently.¹⁴ However, many questions remain, including those related to the gene therapy's long-term efficacy.

VALOCTOGENE ROXAPARVOVEC

Valoctocogene roxaparvec is an investigational gene therapy that is currently being evaluated in two phase III studies for the treatment of hemophilia A.¹⁵ Individuals with hemophilia A have historically been managed with either on-demand or prophylactic administration of intravenous (IV) exogenous factor VIII concentrate. Administration of factor VIII concentrate is associated with frequent IV administration, which may adversely affect patient adherence to therapy. In addition, breakthrough bleeding may occur and may contribute to progressive joint damage. Valoctocogene roxaparvec is an AAV serotype 5 vector that delivers an optimized subcutaneous (SC) variant of B-domain-deleted human factor VIII (AAV5-hFVIII-SQ). Gene transfer through a single IV infusion of valoctocogene roxaparvec may allow individuals with hemophilia to produce therapeutic factor VIII levels, eliminating the need for IV factor VIII concentrate.¹⁵⁻¹⁷ Based on early clinical trial results, treatment with valoctocogene roxaparvec may, in some patients, eliminate or reduce the need for administration of factor VIII concentrate, potentially improving the health and quality of life of those affected by hemophilia A.^{16,17} Overall, in clinical trials, valoctocogene roxaparvec has been well-tolerated by patients across all doses, with the most common adverse events being alanine aminotransferase elevation, arthralgia, aspartate aminotransferase elevation, headache, back pain, fatigue, and upper respiratory tract infection.¹⁸

Gene Silencing: RNAi Therapeutics

RNAi is a natural cellular mechanism in which the gene's own DNA sequence is used to turn off the gene or silence it. RNAi is mediated by small interfering RNA, which functions upstream by silencing messenger RNA, the genetic precursors that encode for proteins associated with disease.¹⁹ By doing so, RNAi therapeutics have the potential to prevent disease-causing proteins from being made.²⁰

PATISIRAN

Patisiran is an investigational orphan drug with the potential to be the first RNAi therapeutic to receive FDA approval.²⁰ Patisiran was evaluated in the phase III APOLLO study (N=225) for its role in the treatment of adults with hereditary amyloidosis transthyretin-mediated (hATTR), an orphan disease caused by mutations in the transthyretin (TTR) gene. Mutations in the TTR gene are associated with abnormal amyloid protein accumulation in the body, leading to organ and tissue damage.²⁰ Although the results have not yet been published, top-line data announced by the manufacturer indicated that the mean change from baseline to 18 months in the modified neuropathy impairment score (mNIS+7) was significantly lower in the patisiran group compared to the placebo. Furthermore, the mean and median changes in mNIS+7 impairment scores each achieved negative values in the patisiran group, which indicates an improvement overall and in the majority of study subjects compared to the baseline. Phase III data suggest patisiran is safe, with peripheral edema and infusion-related reactions being the most commonly reported adverse events. Data suggest that treatment with patisiran reduces symptoms of neuropathological impairment. It is hoped that this translates into clinically meaningful outcomes for patients. If approved, patisiran may offer a convenient route of administration and better speed of onset of efficacy compared to inotersen, another investigational medicine being developed for the treatment of hATTR.²¹

Genome Editing: Use of CRISPR-Cas9 Technology

Genome editing refers to the alteration of a specific DNA sequence within a living cell by cutting a strand of DNA at a specific point, allowing intrinsic cellular repair mechanisms to fix the broken strands, and thereby allowing the repaired strands to affect gene function.¹¹ CRISPR-associated protein 9 has been a significant area of interest for

The high cost of gene therapy raises a larger concern about medical innovation outpacing the ability of payors to cover the cost within the current healthcare payment structure.

pharmaceutical research.²² CRISPR-Cas9 is a targeted nuclease technology containing two key molecules that allow for genome editing with precision. Specifically, the Cas9 component is an enzyme that can cut two strands of DNA at a specified location within the genome so that pieces of DNA can be added or removed. The guide RNA (gRNA) component works by directing the Cas9 enzyme to the target, ensuring that the genome is cut at the correct point. This is achieved by predesigning the gRNA to contain base pairs (typically a sequence of 20 bases) that complement those in the target DNA sequence within the genome.^{22,23} Theoretically, this would result in gRNA that is only able to bind to the target sequence and no other regions of the genome.

Research suggests that the ideal targets for CRISPR-Cas9 genome editing are genetic diseases in which a single allele needs to be targeted, as biallelic targeting is associated with significantly lower efficiency.^{22,23} Currently, more than 10,000 diseases are known to be monogenic, affecting approximately one in 100 births. Some examples of disease states that have been targeted using CRISPR-Cas9 technology in clinical trials include beta thalassemia, cystic fibrosis, hereditary tyrosinemia, human immunodeficiency virus-1 (HIV-1), Duchenne muscular dystrophy, alpha-1 antitrypsin deficiency, polycythemia vera, cataracts, Epstein-Barr virus, and hypercholesterolemia.²⁴

Although great strides have been made in the development of CRISPR-Cas9, there are some significant clinical concerns, including the potential for off-target mutagenesis.²³ As mentioned previously, the gRNA is predesigned to guide Cas9 to the appropriate area in the genome; however, there is potential

for the gRNA to bind to another area in the genome with a similar, but not identical, sequence compared to the target. If this occurs, the Cas9 enzyme may cut at the incorrect site and introduce the mutation in the incorrect location. This error could adversely affect crucial genes, leading to further health concerns.²³ In a clinical trial evaluating CRISPR-Cas9 for the treatment of X-linked severe combined immunodeficiency (also known as “bubble boy” disease), immune systems were successfully restored in most subjects; however, two subjects developed T-cell leukemia more than two years after treatment.^{22,25-27} The researchers determined that the cancers were caused by activation of a cellular oncogene at the site of integration.²² As researchers investigate strategies to limit off-target effects, it will likely be several years before CRISPR-Cas9 technology is routinely used in humans.²⁷

Affordability and Access

While gene therapy, gene silencing, and genome editing represent major medical advancements with the potential to cure serious and/or life-threatening diseases, many of which previously had no treatments available, these advancements also present significant challenges to payors. Voretigene neparvovec, which received FDA approval in December 2017, was unprecedented in both its innovation and its cost. With a price tag of \$850,000 per patient for both eyes, payors were left wondering how they would afford to provide this treatment to the patients who needed it.²⁸ Leading up to the FDA decision, analysts had predicted a cost approaching \$1 million per patient and had even made predictions about alternative payment models, including

amortized payment plans, to help payors better afford the costly therapy.^{29,30} Subsequent to FDA approval, the manufacturer has been working with various health plans to develop solutions that address the issue of extremely high up-front drug costs, including additional rebates from the manufacturer in the event that the therapy is not effective. In addition, multiyear payment plans, in conjunction with rebates in the event that the therapy is not effective, are being discussed.²⁸

The high cost of gene therapy raises a larger concern about medical innovation outpacing the ability of payors to cover the cost within the current healthcare payment structure.³¹ The cost trends in the orphan drug category are alarming. In a 2017 report, analysts noted that the average cost per patient per year in the U.S. for an orphan drug was more than \$140,000 in 2016 compared to approximately \$28,000 for a non-orphan drug.³² Furthermore,

analysts have forecast worldwide orphan drug sales to reach \$209 billion between 2017 and 2022, with an approximate doubling in overall prescription market growth; orphan drugs are predicted to represent 21.4% of worldwide prescription sales by 2022.³²

Concerns about access and affordability are real. The healthcare system is already strained, and these innovations are fundamentally challenging the current system even more. In late 2017, the Institute for Clinical and Economic Review (ICER) published the final version of Orphan Drug Assessment: Final Framework Adaptations. In this publication, ICER noted, “[M]any, but not all, ethicists argue that some preference, some premium, is due to treatments for very rare conditions. But no ethicist, or manufacturer, or clinician, or insurer, or citizen, would argue that treatments for rare conditions should command

avoidance realized when that patient no longer requires costly factor VIII replacement. In the interim, all are left to wonder how the current environment can ensure that there is a system that can drive affordability and access.

Future Directions

The steady stream of genetic discoveries and new genetic tests made possible by the Human Genome Project shows no signs of abating and is expected to only increase in the coming years. While advancements in technology usher in a new wave of medical innovation, it is clear that the economics of healthcare in the U.S. will need to adapt in order to support and promote these breakthroughs. Payors will likely continue to be at the forefront and should continue to develop and propose out-of-the-box strategies to ensure that they are able to provide

TABLE 1. SNAPSHOT OF SELECT LATE-STAGE PIPELINE AGENTS FOR ORPHAN DISEASES	
Drug Name	Indication
AVXS-101	SMA type 1
Crizanlizumab	Sickle cell anemia
Fitusiran	Hemophilia A and B
GS010	Leber’s hereditary optic neuropathy
Inotersen	hATTR
Lenti-D	CCALD
Mogamulizumab	CTCL
Patisiran	hATTR
Pegvaliase	PKU
Valoctocogene roxaparvovec	Hemophilia A
VB-111	Recurrent glioblastoma and anaplastic astrocytoma

Abbreviations: CCALD = childhood cerebral adrenoleukodystrophy; CTCL = cutaneous T-cell lymphoma; hATTR = hereditary amyloidosis transthyretin-mediated; PKU = phenylketonuria; SMA = spinal muscular atrophy

Payors, pharmaceutical companies, employers, pharmacy benefit managers, government agencies, and patients will need to come together to ensure that innovation, and the costs that come with innovation, can be sustained.

an unlimited premium. To decide how much preference, how high the price for a treatment should go, is a question whose answer requires us to find an elusive balance between two different views of fairness.”³³

Payors are dealing with this issue by closely evaluating the value that a new therapy provides compared to the cost, taking into consideration whether the therapy is potentially curative or provides a benefit in quality of life. If the therapy is curative, it is important to consider the cost avoidance that may result from discontinuing chronic medications for that disease. For example, if treatment with valoctocogene roxaparvovec cures a patient of hemophilia A, there may be significant cost

these therapies to the patients who need them most. Payors, pharmaceutical companies, employers, pharmacy benefit managers, government agencies, and patients will need to come together to ensure that innovation, and the costs that come with innovation, can be sustained.

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Key Opinion Leaders:

The Value of Experts in Peer-to-Peer Discussions and Second Opinions

One of the greatest challenges in managed care is remaining up to speed on the various changes that occur in the constantly evolving healthcare landscape. These changes may include, but are not limited to, updates to clinical practice guidelines and the availability of new-to-market therapies for high-cost, common disease states and novel treatments for complex, rare diseases for which treatments did not previously exist. Physicians and payors are tasked with staying up-to-date on the newest innovations and clinical approaches, which can be overwhelming, particularly for rare disease states.



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Additionally, payors are faced with making difficult clinical coverage decisions for hundreds of disease states in which the management landscape changes frequently and to varying degrees. This can be an enormous challenge for payors as they must also juggle competing tasks and priorities, such as managing drug spend, developing clinical programs, and implementing effective member engagement strategies.

Payors report difficulties surrounding the receipt of inappropriate requests, particularly off-label use requests for specialty drugs in high-cost, rare disease categories, which are poorly understood and for which clinical practice guidelines may not exist or are unclear. In these instances, seeking a second opinion and insight from an expert in the respective field can be extremely valuable to payors, providers, and patients alike. To address this unmet need, some payors seek the assistance of key opinion leaders (KOLs), also known as thought leaders.

KOLs are considered experts in their respective fields, and many managed care organizations depend on them to better understand specific disease states and new therapies. A 2009 Market Strategies International research study of a select group of 100 national and regional KOLs revealed that respondents defined a KOL according to the following key characteristics:

- 1 Regularly sought out by their colleagues for opinions or advice
- 2 Speak often at regional or national conferences
- 3 Have published articles in a major journal during the past two years
- 4 Consider themselves early adopters of new treatments or procedures
- 5 Help establish protocols for patient care

As part of its value-based approach to medical and pharmacy benefit management, Magellan Rx Management offers the KOL Services Program to assist

in both specialty and non-specialty disease management, especially in high-spend disease categories, such as inflammatory conditions, oncology and oncology support, hepatitis C, intravenous immune globulin, and orphan diseases. Magellan Rx Management has a clinical advisory panel of local, national, and world-renowned experts and has access to more than 100 key thought leaders in a number of disease categories, ranging from common conditions such as diabetes to rare conditions including hereditary angioedema, pulmonary arterial hypertension, hemophilia, and Gaucher's disease. Figure 1 displays a sampling of the various major centers nationwide with which Magellan's KOLs are affiliated. Figure 2 provides a breakdown of disease categories for which KOLs have assisted in reviews.

The KOL Services Program includes the provision of insights and consultation in pharmacy and therapeutics (P&T) committee meetings, new drug reviews, treatment guidelines, current standards of care, development of clinical programs, prior authorization (PA) case review, appealed PA cases, peer-to-peer discussions, medical policy development, preferred product selection, and formulary development. Instead of simply denying inappropriate requests, Magellan Rx Management arranges for peer-to-peer consultations with KOLs and requesting physicians. KOL consultations can help avoid inappropriate use of drugs based on diagnosis or dose and can lead to hundreds of thousands of dollars in costs avoided over time. Peer-to-peer conversations between KOLs and requesting prescribers may also lead to clinical withdrawals of potentially inappropriate therapy and can help ensure patients get appropriate treatment, when applicable.

Through the KOL Services Program, Magellan Rx Management provided 223 KOL reviews for one regional client over three years. This included 197 case reviews, 24 of which included peer-to-peer reviews, and 26 policy or drug information reviews. Of these, 73 KOL recommendations (36.5% of

FIGURE 1. OUR KOLs ARE AFFILIATED WITH MAJOR CENTERS NATIONWIDE

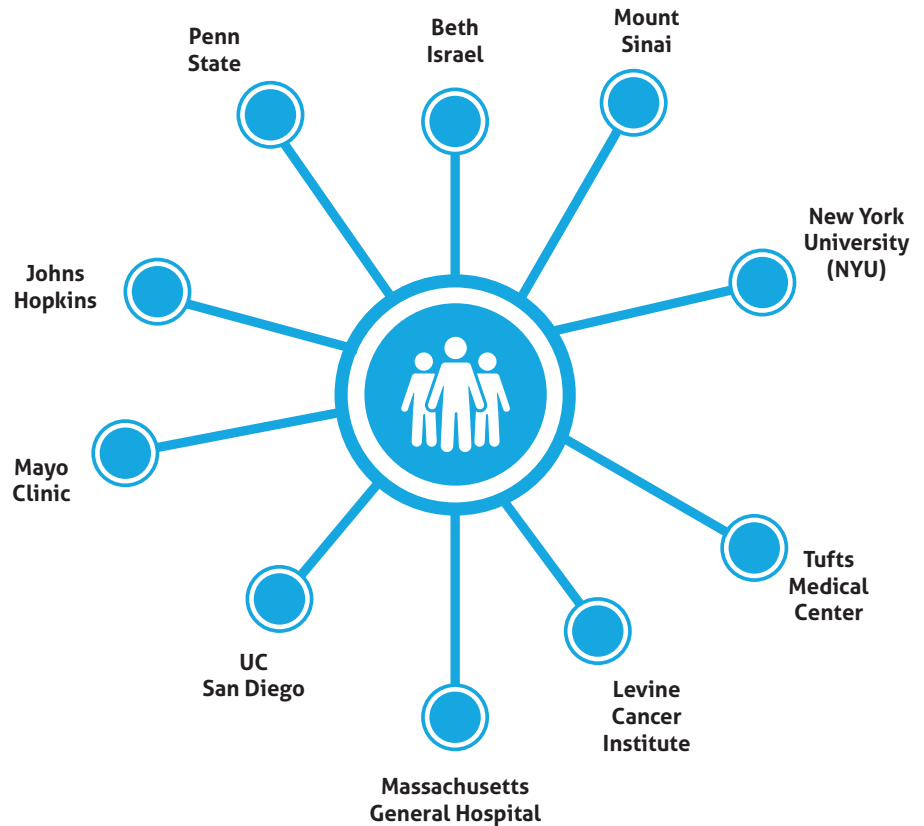


FIGURE 2. KOL REVIEWS BY DISEASE CATEGORY

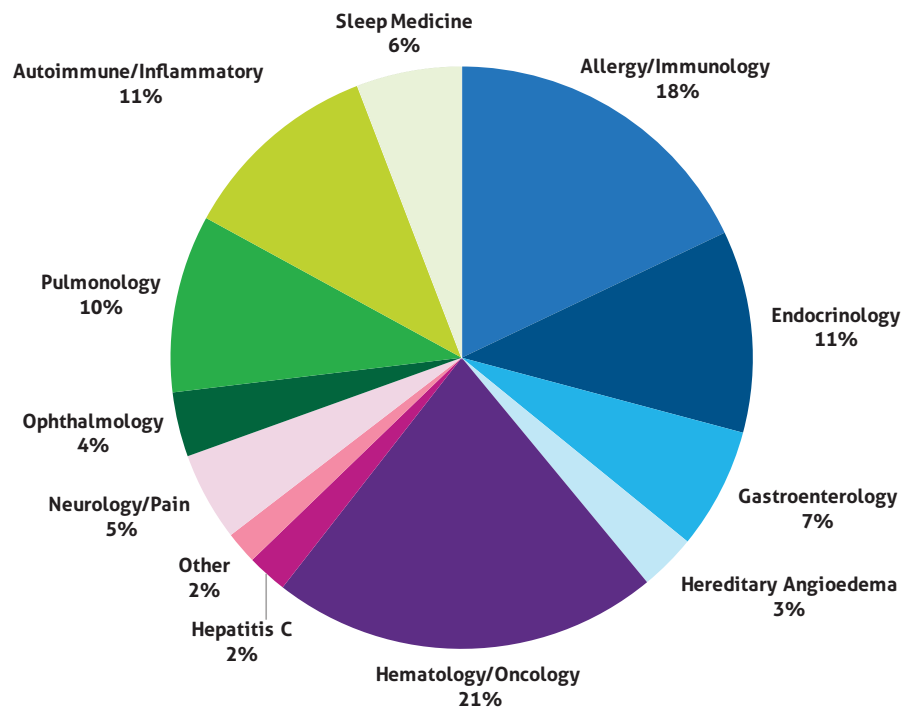


FIGURE 3. KOL SERVICE CASE EXAMPLE 1

OUTCOME



Cuprimine dose increase denied



Potential harmful side effects avoided



Estimated savings of
\$23.5K per month

FIGURE 4. KOL SERVICE CASE EXAMPLE 2

OUTCOME



Denial overturned and Onfi was approved for this patient



KOL was able to provide a validated second opinion to support the complex treatment of patient with severe disease

case reviews) led to potential savings through the following:

- 34% alternate therapy recommended
- 12% dose optimization recommended
- 54% treatment determined to be clinically inappropriate

One example of a KOL service case was a client request for a dose increase for a patient with recurring kidney stones due to underlying cystinuria. The KOL was consulted and provided an evidence-based recommendation that resulted in a dose increase denial, avoidance of harmful side effects for the patient, and an estimated savings of \$23,500 per month. Figure 3 highlights this case example.

A second example of a KOL service

case was a client request for treatment continuation in a patient with complex partial seizures and who was being managed with five different medications for breakthrough seizures. Despite therapy, the patient experienced 20 breakthrough seizures over the prior two-month period. Based on perceived lack of efficacy, the client denied the request but sought KOL assistance in reviewing the decision to determine appropriateness of treatment continuation. The KOL was consulted and provided an evidence-based recommendation that resulted in an overturned denial and medication continuation approval for the patient. Figure 4 highlights this case example.

Partnering with Magellan Rx Management keeps our clients on the

cutting edge of disease management by focusing on providing the highest level of expertise and quality of care. The KOL Services Program aims to reduce inappropriate use of medications, while offering the highest value and quality of care in disease management. As always, we appreciate our current partnerships, and we look forward to creating new and industry-leading solutions for our clients in the year to come.

Better Health, Brighter Future



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Takeda is a patient-focused global pharmaceutical company that builds on a distinguished 237-year history of leading innovation in medicine.

Driven by the needs of our patients, Takeda is dedicated to improving access to our medicines and supporting long-lasting value-based care. Through strategic thinking and collaboration, Takeda seeks to develop solutions to the issues faced by health plans today.

With our breadth of expertise and experience, **Takeda is committed to partnering with you to make a positive impact on the future of healthcare.**

Alzheimer's Disease:

What's in the Pipeline?

Alzheimer's disease (AD) is an irreversible, progressive, neurodegenerative disease that impacts memory, cognition, and function.¹ AD is the most common cause of dementia among older adults and can range from mild to severe, with increasing severity resulting in reduction in the ability to complete activities of daily living (ADLs).¹



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In the U.S., there are approximately 5.4 million cases of AD.² By the year 2050, there will be a projected doubling in the annual number of new cases of AD and other dementias, and 13.8 million Americans aged 65 and older may have AD.²

There is no cure for AD and there are no disease-modifying treatments available at this time. The current treatment landscape for AD consists of cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists, and a combination product of a cholinesterase inhibitor and NMDA receptor antagonist (see Figure 1).

Unfortunately, there is a high failure rate among investigational agents. From 2002 to 2012, 244 drugs were tested in clinical trials, and only one received Food and Drug Administration (FDA) approval.³

There is a large unmet need for an effective AD treatment from a clinical, humanistic, and economic perspective.

In 2017, the aggregate cost of care in AD was \$259 billion, with the total cost of care projected to jump to \$1.1 trillion by the year 2050 based on disease trajectory estimates.^{2,4} The majority of this spending (\$131 billion) comes from Medicare, followed by out-of-pocket expenses (\$56 billion), Medicaid spend (\$44 billion), and other expenditures (\$28 billion).² If an effective treatment that could delay AD onset by five years launches in 2025, Medicare, Medicaid, and the federal and state governments' cumulative savings would be \$67 billion, \$38 billion, and \$535 billion, respectively, by 2035.⁵

Currently there are a handful of investigational drugs that are being studied in phase III trials for the treatment of AD. The most noteworthy agents include aducanumab, AVP-786 (deuterated dextromethorphan and quinidine), azeliragon, brexpiprazole, crenezumab, gantenerumab, and LMTX. These investigational drugs will be discussed below.

ADUCANUMAB

Aducanumab (Biogen Inc.) is an intravenous (IV) anti-beta-amyloid antibody that is being studied for the treatment of early AD and prodromal AD. In the 24-month, phase Ib PRIME study, once prodromal patients were switched from placebo to aducanumab, they showed declines in plaque burden and slower rates of cognitive/functional decline.⁶⁻⁸ Furthermore, patients who started on the active drug and remained on it saw



continued benefits and a more significant response than those who started on placebo and switched to the active drug.⁶⁻⁸ In PRIME, the most common adverse effect was amyloid-related imaging abnormalities (ARIA), which occurred at a higher rate in ApoE4 carriers and with higher doses of the drug.⁶⁻⁸ Aducanumab is being studied in the ongoing, long-term, phase III EMERGE and ENGAGE trials, and the manufacturer recently announced that it would add approximately 500 more patients to these studies, which have expected full results in 2020.⁹ The FDA granted aducanumab fast track designation in September.¹⁰

AVP-786

AVP-786 (Otsuka Holdings Co. Ltd., Avanir Pharmaceuticals, and Concert Pharmaceuticals) is an oral NMDA receptor antagonist, sigma-1 receptor agonist, and serotonin and norepinephrine transport inhibitor being studied for the treatment of agitation in AD.¹¹ This investigational agent is currently being studied in the phase III TRIAD1 and TRIAD2

trials, which have estimated completion dates in 2019, and anticipated interim data readouts in 2018.¹² In a phase I trial, data demonstrated that AVP-786 has a similar safety and efficacy profile to AVP-923: a combination of dextromethorphan and a higher dose of quinidine than AVP-786.¹¹ AVP-786 was granted fast track designation by the FDA. Of note, among the 5.4 million Americans with AD, approximately 50% of them exhibit agitation symptoms, highlighting the large population for whom this treatment may fill a large unmet need.^{2,13}

AZELIRAGON

Azeliragon (vTv Therapeutics Inc.) is an oral receptor for advanced glycation endproducts (RAGE) antagonist being studied for the treatment of mild AD.¹⁴ In a phase IIb trial, an interim futility analysis revealed there was a lack of response at the 5 mg dose; but the study was carried to completion, and treatment with azeliragon showed a statistically significant benefit in mild to moderate AD patients.¹⁴ Improvements were also observed on secondary endpoints,

including a statistically significant reduction in psychotic adverse events in the active treatment group.¹⁴ Enrollment for the ongoing phase III STEADFAST trial was completed in June 2017, with expected data readouts in early 2018 and late 2018 for parts A and B, respectively.¹⁵ If trials are successful, the company may submit a new drug application (NDA) by the end of 2018.¹⁵ In clinical trials, azeliragon was associated with adverse effects, including fall, upper respiratory tract infection, headache, and urinary tract infection. Azeliragon was granted fast track designation by the FDA and is the only clinical stage RAGE inhibitor.

BREXPIPIRAZOLE

Brexpiprazole (Otsuka Holdings Co. Ltd. and H. Lundbeck A/S) is an oral agent being studied for the treatment of agitation in AD and is presently FDA-approved for the treatment of major depressive disorder and schizophrenia.¹⁶ In 2017, the results of both phase III trials were announced, and patients treated with brexpiprazole showed improvements in symptoms of agitation compared to placebo.¹⁶ In clinical trials, brexpiprazole has been associated with insomnia, agitation, and somnolence.¹⁶ In the first half of 2018, an additional phase III trial is expected to begin in patients with dementia of the Alzheimer's type.

CRENEZUMAB

Crenezumab (Roche) is a subcutaneous (SC)/IV humanized monoclonal antibody that binds to amyloid beta and is being studied for the treatment of prodromal and mild AD. Phase II trials of crenezumab, ABBY and BLAZE, in mild to moderate AD failed to meet co-primary endpoints and demonstrated no significant effects on cognitive or

FIGURE 1. CURRENT TREATMENT LANDSCAPE IN AD

Cholinesterase Inhibitors	donepezil, galantamine, galantamine ER, rivastigmine
NMDA Receptor Antagonists	memantine, memantine ER
Combination Product	donepezil-memantine

functional endpoints with 15 mg/kg dosing.¹⁷ To address the lack of benefit with lower dosing, higher dosing (60 mg/kg) is being used in two identical phase III trials — CREAD and CREAD2 — which have data readouts expected in 2020 or 2021.^{17,18} Adverse effects in trials were generally mild to moderate and transient and did not appear to be related to treatment.¹⁷ An imbalance in the rate of serious and non-serious events of pneumonia (3.2% vs. 0.6% for crenezumab and placebo, respectively) was observed; however, this rate is consistent with the rate of expected cases of pneumonia among older patients, and no drug-related mechanism for pneumonia was identified. Crenezumab was granted fast track designation in 2016, and the manufacturer has announced it may file for approval in 2020 or later.^{19,20}

GANTENERUMAB

Gantenerumab (Roche and MorphoSys) is an SC/IV humanized monoclonal antibody that targets amyloid beta and is being studied for the treatment of prodromal to mild AD and in at-risk patients with an inherited autosomal dominant mutation in amyloid precursor protein (APP)/presenilin (PS)-1 or APP/PS-2. The previous phase III SCarlet RoAD trial in prodromal patients was discontinued after a pre-specified futility analysis. There is an ongoing phase III Marguerite RoAD trial in patients with mild AD and a second ongoing DIAN-TU trial in patients who are at risk of dominantly inherited AD. Additionally, two pivotal phase III studies were initiated in 2017 in patients with prodromal to mild AD.²¹ Similar to aducanumab, gantenerumab was associated with ARIA in clinical trials.²¹

LMTX

LMTX (TauRx Therapeutics Ltd.) is an oral second-generation tau aggregation inhibitor that is being studied for the treatment of mild to moderate AD.²² Two phase III global trials evaluated treatment with LMTX in patients with mild to moderate AD. In one of the phase III trials, there were no observed effects on brain atrophy levels. However, a subgroup analysis of LMTX treatment

If an effective treatment that could delay AD onset by five years launches in 2025, Medicare, Medicaid, and the federal and state governments' cumulative savings would be \$67 billion, \$38 billion, and \$535 billion, respectively, by 2035.

in monotherapy patients (i.e., those not receiving concomitant memantine or cholinesterase inhibitors) demonstrated statistically significant improvements on cognitive and functional outcomes compared to placebo and significant effects on brain atrophy levels. More recently, the results of the second ongoing phase III trial were released, and the results were consistent with those observed from the first phase III study.²² In the most recent study, after nine months of treatment, the annualized rate of whole brain atrophy in LMTX monotherapy patients reduced significantly and became typical of that reported in normal elderly controls without AD; the comparable rate observed in the add-on therapy group progressed as reported for patients with mild AD.²² Additional studies are planned in the coming months.²² In clinical trials, gastrointestinal and urinary effects were the most commonly observed adverse events with high doses of treatment and the most common causes for discontinuation; however, these events were typically mild in nature and easily controlled. LMTX is unique in that it targets the tau protein and may offer disease-modification benefits, thereby differentiating it from other pipeline agents in development.

Conclusion

With a nearly 100% failure rate in the AD treatment pipeline over the last 15 years, these phase III investigational agents may offer hope to patients, caregivers, and clinicians who have been patiently waiting for an effective treatment to become available. Although none of these treatments

have been submitted for FDA review at the time of this writing, it is possible that at least one of these treatments may receive FDA approval within the next 12 to 24 months.

The FDA recently released draft guidance for industry surrounding the development of drugs for the treatment of early AD.²³ The draft was one of five proposals released by the FDA in February to help increase development of treatments for neurological diseases. Although still in draft form and therefore not yet implemented, the changes proposed could help stimulate research efforts for AD drugs. However, it is important to note that the proposed changes would also involve risk, as these changes would permit using products that may be studied using cognition-only endpoints; in other words, they would not have the same scientific evidence for use that is associated with products studied in trials that have historically measured symptoms such as memory and function loss.^{23,24} The comment period on the draft guidance will remain open until May 17, 2018.

While the prospect of a new treatment is exciting for many, a potential approval also comes with challenges, particularly how to pay for these treatments, which are anticipated to be very expensive. Payors are encouraged to remain up-to-date regarding any regulatory progress made in this therapeutic class and to prepare themselves for the anticipated large budgetary impact any of these agents may have on their organizations.

FIGURE 2. DRUGS TO WATCH IN AD

Drug Name	Route of Administration	Mechanism of Action
Aducanumab	IV	Anti-A β antibody
AVP-786	Oral	Multiple
Azeliragon	Oral	RAGE antagonist
Brexiprazole	Oral	Unknown
Crenezumab	IV/SC	Anti-A β antibody
Gantenerumab	IV/SC	Anti-A β antibody
LMTX	Oral	Second-generation TAI

Abbreviations: A β = amyloid beta; IV = intravenous; RAGE = receptor for advanced glycation endproducts; SC = subcutaneous; TAI = tau aggregation inhibitor

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The Opioid Crisis:

A Legislative Update

In 2016, more than 42,000 people in the U.S. died as a result of opioid use, including the use of prescription opioids, heroin, and fentanyl. This number rose above the opioid-related death rate of any year on record.¹ Every day, 91 Americans die from opioid overdose, and 40% of these overdoses result from prescription opioid use.¹ Since 1999, deaths from prescription opioids have more than quadrupled, turning this crisis into an epidemic. The amount of prescription opioids sold to healthcare facilities and pharmacies nearly quadrupled between 1999 and 2010 — a disproportionate increase compared to the stagnant amount of pain reported by Americans.^{2,3}



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In an effort to combat the rising rate of prescription opioid use, the Centers for Disease Control and Prevention (CDC) issued a Guideline for Prescribing Opioids for Chronic Pain in 2016. The guideline includes 12 recommendations, but three principles are identified as crucial to improving patient care surrounding pain management:⁴

- 1 Nonopioid therapy is preferred for chronic pain outside of active cancer, palliative, and end-of-life care.
- 2 When opioids are used, the lowest possible effective dosage should be prescribed to reduce risks of opioid use disorder and overdose.
- 3 Clinicians should always exercise

caution when prescribing opioids and monitor all patients closely.

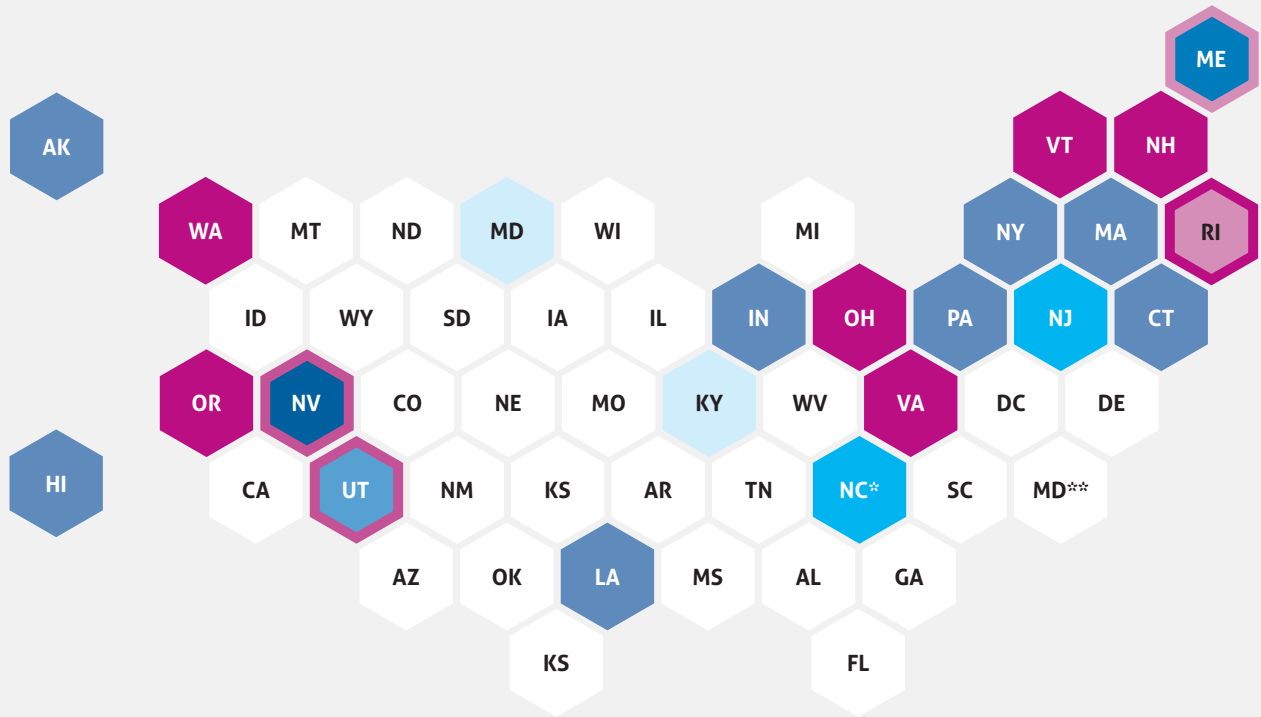
While federal efforts are an important step, it is crucial that this health crisis be addressed at the state level. The CDC has outlined certain promising strategies that states could utilize in an effort to manage this epidemic and provide effective solutions. Some of these strategies include optimizing the use of prescription drug monitoring programs (PDMPs), adopting policies that manage prescribing practices at pain clinics, increasing access to substance abuse treatment services and programs, expanding first responder access to naloxone, and promoting the use of the CDC Guideline for Prescribing Opioids for Chronic Pain.⁵

Prescribing Limits on Opioids

The most common state effort to combat the opioid epidemic is regulation of prescribing limits for opioids. This type of legislation first appeared in early 2016 when Massachusetts passed the first in the nation, limiting initial opioid prescriptions to a seven-day supply.⁶ By July 2017, 23 states had enacted legislation with some type of limitation, guidance, or requirement pertaining to opioid prescribing.⁶

This type of state legislation generally takes the form of limiting first-time opioid prescriptions to a certain number of days' supply. In about half of the states, the limitations are explicitly applied to treating acute pain, with most states allowing exceptions for chronic pain

FIGURE 1. LAWS SETTING LIMITS ON CERTAIN OPIOID PRESCRIPTIONS



- Statutory limit: 14 days
- Statutory limit: 7 days
- Statutory limit: 5 days
- Statutory limit: 3-4 days
- Statutory limit: morphine milligram equivalents (MME)
- Direction or authorization to other entity to set limits or guidelines
- No limits

AS GU MP PR VI

No information

* North Carolina's 5-day limit is for acute pain. The state also set a 7-day limit for post-operative relief.

** Maryland requires lowest effective dose in a quantity not greater than that needed for expected duration of pain.

treatment, hospice, and palliative care.⁶ The most common prescribing limit is seven days, while Kentucky and Minnesota have prescribing limits as low as three to four days. Of the states with this type of legislation, Nevada is the least restricted, with a 14-day statutory limit.

In a few states, such as Rhode Island, legislation has been passed setting dosage limits (morphine milligram equivalents, or MMEs). According to the CDC, the MME prescribed per person in 2015 was more than three times as high as in 1999. The organization recommends starting with the lowest effective dose of immediate-release opioids.⁷ In an effort to address CDC concerns and implement recommendations, states like Rhode Island, Nevada, and Maine have established dosage limits.⁶

Prescription Drug Monitoring Programs

A popular approach to the opioid crisis for states is passing legislation or regulations regarding the use of PDMPs, or statewide electronic data systems that collect, analyze, and make available prescription data on controlled substances dispensed by non-hospital pharmacies and practitioners.⁸ PDMP data help states track opioid prescribing and can reveal prescribing rates for controlled substances; providers and/or pharmacies who are prescribing and/or dispensing controlled substances in excessive quantities; individuals who are prescribed dangerous combinations of controlled substances; and individuals who may be doctor or pharmacy shopping or are receiving multiple prescriptions for commonly misused drugs from multiple

Virginia legislation requires that dispensing information is submitted within 24 hours of dispensing and allows a prescriber or dispenser to re-disclose PDMP information to another prescriber or dispenser; it also allows the PDMP information to be filed in patients' medical records.

prescribers and/or pharmacies.⁸ Legislation relating to PDMPs takes various forms on the state level, including expanding access to PDMP information, mandatory PDMP enrollment or checks, and reducing transmission frequency.⁹

Some states such as Arkansas, Florida, New Hampshire, and Virginia, have expanded access to PDMP information. In Arkansas, legislation was passed in 2016 establishing requirements for law enforcement to access PDMP information, while Virginia legislation allows disclosure of PDMP information to a prescriber for the purposes of establishing treatment history while the patient is under said prescriber's care.⁹ The Virginia legislation, which was passed in January 2017, also allows PDMP information to be disclosed in an effort to assist a dispenser in confirming the validity of a prescription or for purposes of consultation with a patient.⁹

States are also passing legislation creating mandatory PDMP enrollment requirements. In Alabama, all medical directors of pain management clinics

must have current PDMP registration; and in Mississippi, all licensed pharmacists must register with the PDMP.⁹ Other states have legislated mandatory checks of PDMP.⁸ For example, New York legislation requires opioid treatment programs to check the PDMP prior to admitting new patients.¹⁰ New Hampshire, New Mexico, and Virginia all have variations of legislation requiring prescribers and practitioners to request and/or obtain PDMP information when prescribing initial opioid prescriptions.⁹ Virginia legislation requires that dispensing information is submitted within 24 hours of dispensing and allows a prescriber or dispenser to re-disclose PDMP information to another prescriber or dispenser; it also allows the PDMP information to be filed in patients' medical records.^{11,12}

Removing Barriers to Opioid Dependence-Related Treatment

Some states have focused on creating broad legislation targeting many approaches to manage the opioid crisis. This type of legislation often includes an effort to increase ease of access to critical treatments to improve quality of life for those suffering from opioid dependence.

Comprehensive legislation passed in New York addressed burdensome barriers to access for inpatient treatment and medication for opioid dependence.¹⁰ Previously, insurance companies were able to implement prior authorization and referral requirements for these treatments, which delayed timely

The most common prescribing limit is seven days, while Kentucky and Minnesota have prescribing limits as low as three to four days. Of the states with this type of legislation, Nevada is the least restricted, with a 14-day statutory limit.



access to substance abuse treatment. The legislation now requires insurance companies to cover these treatments for 14 days prior to any utilization management strategy being implemented, thus allowing for immediate access to inpatient treatment and greater access to drug treatment medications.¹⁰ Along with mandating insurance coverage for opioid overdose-reversal medications, the legislation also requires that all insurance companies use objective state-approved criteria to determine the level of care for individuals suffering from substance abuse.¹⁰

Delaware also passed legislation preventing insurers from using strategies that delay access to substance abuse treatment and requiring insurers to cover 14 days of substance abuse treatment before conducting utilization review.¹³ The Delaware legislation also limits insurance companies from denying treatment for substance abuse on the grounds of “medical necessity.”¹³

Overdose Immunity, Naloxone Access, and Good Samaritan Laws

Access to the FDA-approved “rescue drug” naloxone was limited until state legislatures provided statutory protections for individuals other than medical professionals to possess and

administer the drug without a prescription.¹⁴ A “third-party” prescription, which provides medication to some-

Federal guidelines are valuable in advising states on what strategies may work in terms of managing opioid use, but, ultimately, states are more suited to construct legislation that works in terms of each state’s specific population and needs.

one other than the individual misusing drugs, was typically prohibited by laws that required a doctor-patient relationship prior to a prescription.¹⁴ In 2001, New Mexico enacted legislation increasing access to naloxone.¹⁴ By July 2017, all 50 states had enacted legislation allowing laypersons access to the overdose-reversal treatment.¹⁵ In 2014, more than 150,000 laypersons had access to naloxone prescriptions resulting in more than 26,000 overdose reversals.^{14,16} Characteristics of naloxone access laws often include any combination of the following: civil and

criminal immunity for prescribers, dispensers, and lay administrators; disciplinary immunity for prescribers and dispensers; access to laypersons for distribution and possession; and permitted standing prescription orders and/or third-party prescribing.¹⁵ The National Bureau of Economic Research has found that a naloxone access law is associated with a 9% to 11% decrease in opioid-related deaths in its respective state.¹⁵

In an effort to encourage individuals to seek medical attention and assistance from first responders in the case of an overdose, a vast majority of states have passed Good Samaritan or immunity laws.^{14,15} As of 2017, 40 states passed legislation that provides immunity from arrest, charges, and/or prosecution for drug-related offenses, such as possession or paraphernalia, for those calling 9-1-1 when an overdose is occurring.^{14,15} Good Samaritan laws

vary by state in terms of leniency. Other immunities or protections offered by these laws may include immunity relating to protective or restraining orders and pretrial, probation, or parole conditions.¹⁵ The ultimate purpose of these laws is to remove any barriers creating any anxiety or hesitation for an individual who is in a position to contact first responders in the event of an overdose. Less liability and risk on the part of a 9-1-1 caller will incentivize more individuals to seek medical assistance and decrease preventable opioid overdose-related deaths.



Moving Forward

States are on the front lines in combating the opioid epidemic. The trend of state efforts to regulate the prescribing of opioids and manage the current crisis is set to persist as this type of legislation continues to show a positive impact

on communities. Federal guidelines are valuable in advising states on what strategies may work in terms of managing opioid use, but, ultimately, states are more suited to construct legislation that works in terms of each state's specific population and needs. While legislation

is not a cure-all for the opioid epidemic, it is a step toward resolving an evolving health and drug crisis with state action.

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Migraine:

Pipeline and Treatment Landscape Update

Migraine continues to be a poorly understood disease that is often undiagnosed and undertreated.^{1,2} More than half of all migraine sufferers are never diagnosed, while the vast majority of those who are diagnosed do not seek medical care for their pain.

Migraine treatment approaches are generally guided by several factors:

- 1 Severity of attacks
- 2 Presence of nausea and/or vomiting
- 3 Treatment setting (medical care facility vs. outpatient)
- 4 Patient-specific factors (e.g. vascular risk factors, drug preference, costs, etc.)

Several guidelines are available to help navigate the diagnosis and treatment of migraine.³⁻⁶ Symptomatic treatment of migraine involves potential options including nonsteroidal anti-inflammatory drugs (NSAIDs), dopamine antagonists, corticosteroids, opioids, antiemetics, triptans, and various combinations of these classes.^{6,7}

A number of investigational drugs are currently in development for the treatment of migraine, some of which are discussed in further detail below.

Serotonin Receptor Agonist Therapy

Lasmiditan, a non-triptan serotonin 1F (5-HT_{1F}) receptor agonist, has shown

efficacy in treating acute migraine in the phase III SAMURAI and SPARTAN studies, while one other phase III study (GLADIATOR) is underway. In SAMURAI, freedom from migraine pain two hours after dosing was significantly higher with lasmiditan 100 mg and 200 mg compared to placebo (28.2%, 32.2%, and 15.3%, respectively).⁸ In SPARTAN, the study met its primary endpoint by demonstrating that more patients treated with lasmiditan were free of migraine pain compared to placebo at two hours following the first dose, with statistically significant results across the 50 mg, 100 mg, and 200 mg studied doses.⁹ By targeting the 5-HT_{1F} receptor, which does not cause vasoconstriction, lasmiditan may avoid the cardiovascular and cerebrovascular effects associated with triptans, which target 5-HT_{1B/1D} receptors and work through vasoconstriction.^{10,11} In a press release, Lilly announced its plans to submit a new drug application (NDA) for lasmiditan in the second half of 2018.⁹

Anti-CGRP Monoclonal Antibodies

The inhibition of calcitonin gene-related peptide (CGRP) has become a novel area of treatment. Monoclonal antibodies (mAbs) against CGRP or its receptor have gained significant interest in recent years. At this time, four mAbs targeting CGRP or its receptor (galcanezumab, eptinezumab, fremanezumab, and erenumab) are in phase III trials for migraine, while the small-molecule CGRP antagonist atogepant is being investigated for migraine prevention.

GALCANEZUMAB (LILLY)

In a phase III study, treatment with self-administered galcanezumab for up to 12 months demonstrated a positive safety and tolerability profile in patients with migraine.¹² These findings were consistent with results observed in previous studies with the investigational drug. Over the 12-month treatment period, treatment with galcanezumab was associated with a reduction in the number of monthly migraine headache days with the 120 mg and 240 mg doses (5.6 days and 6.5 days, respectively, $P < 0.001$ for both dosing groups).¹² In December 2017, the Food and Drug Administration (FDA) accepted the biologics license application (BLA) for galcanezumab for the prevention of migraine in adults, and a decision is expected in 2018.¹³

While 25% of migraine sufferers would benefit from preventive treatment, only 12% of them receive it.

EPTINEZUMAB (ALDER BIOPHARMACEUTICALS)

The phase III PROMISE 1 study met its primary endpoint by demonstrating reductions in monthly migraine days from baseline (8.6 days on average) in patients treated with eptinezumab 300 mg (4.3 days, $P=0.0001$) and 100 mg (3.9 days, $P=0.0179$) compared to placebo (3.2 days).¹⁴ At least a 75% reduction in monthly migraine days was achieved over weeks one through four in the 300 mg (31.5%, $P=0.0066$) and 100 mg groups (30.8%, $P=0.0112$) compared to placebo (20.3%).¹⁴ A reduction of at least 75% in monthly migraine days was also achieved over weeks one through 12 among 29.7% of patients in the 300 mg dosing group ($P=0.0007$) compared to 16.2% of patients in the placebo group.¹⁴ Alder BioPharmaceuticals announced that top-line data for a second phase III study (PROMISE 2) are expected in the first half of 2018; and the results of the two studies will be used to support a BLA submission for eptinezumab, with planned filing in the second half of 2018.¹⁴

FREMANEZUMAB (TEVA PHARMACEUTICAL INDUSTRIES LTD.)

In a phase III study, treatment with fremanezumab reduced the number of days patients experienced a headache by an average of 4.3 days with quarterly treatment and 4.6 days with monthly treatment.¹⁵ Among patients on the monthly and quarterly regimens, 37.6% and 40.8% of patients, respectively, achieved at least a 50% reduction in the number of moderate headaches they experienced per month, compared to 18.1% of patients in the placebo group.¹⁵ An FDA decision is expected in mid-2018.¹⁶ Recently, the FDA issued a warning letter to the plant that makes the active pharmaceutical ingredient (API) for the fremanezumab

injection; however, the CEO of Teva explained that the API is not affected by the warning letter, so the FDA decision timeline may or may not be affected by this FDA communication.

ERENUMAB (AMGEN AND NOVARTIS)

The phase III STRIVE study met its primary endpoint by demonstrating that patients receiving treatment with erenumab 140 mg or 70 mg once monthly experienced a reduction in monthly migraine days compared to placebo (3.7-day reduction for 140 mg and 3.2-day reduction for 70 mg vs. 1.8-day reduction for placebo, $P<0.001$ for both).¹⁷ Additionally, half of the patients in the erenumab 140 mg dosing arm experienced at least a 50% reduction in their migraine days.¹⁷ The recent phase IIIb LIBERTY study met its primary endpoint by demonstrating that significantly more patients who were treated with erenumab had at least a 50% reduction from baseline in their monthly migraine days compared to placebo; the study also met all secondary endpoints.¹⁸ An FDA decision is expected on May 17, 2018.

Oral CGRP Receptor Antagonist UBROGEPANT (ALLERGAN)

In ACHIEVE I ($N=1,327$), the first of two pivotal phase III clinical trials, the safety, efficacy, and tolerability of oral ubrogepant 50 mg and 100 mg were evaluated compared to placebo in a single migraine attack of moderate to severe headache intensity in adults.¹⁹ Treatment with both doses demonstrated a greater percentage of patients achieving freedom from pain at two hours after the initial dose compared to placebo (50 mg vs. placebo, $P=0.0023$; 100 mg vs. placebo, $P=0.0003$) and a greater percentage of patients achieving absence of the most bothersome migraine-associated symptom

(including photophobia, phonophobia, or nausea) at two hours after the initial dose compared to placebo (50 mg vs. placebo, $P=0.0023$; 100 mg vs. placebo, $P=0.0023$).¹⁹ In this study, treatment with ubrogepant was well-tolerated and demonstrated an adverse event profile similar to placebo, with the most common adverse events including nausea, somnolence, and dry mouth (each reported with a frequency of $\leq 5\%$).¹⁹ Additional results are anticipated to be released in 2018, and results of the second phase III trial — ACHIEVE II — are expected in the first half of 2018.¹⁹ The manufacturer has announced that it anticipates filing an NDA in 2019.¹⁹

Neuromodulation

Methods such as transcutaneous supraorbital nerve stimulation have been found to be effective in episodic migraine prevention, while vagus nerve stimulation has been found to be effective in treating acute migraine. Therapeutic targets include the cerebral cortex, occipital nerves (including trigeminal nerve branches and vagus nerves), cranial nerves, and the trigeminal nucleus caudalis in the high cervical spinal cord.

GAMMACORE (NON-INVASIVE VAGUS NERVE STIMULATOR [nVNS])

In April 2017, gammaCore received FDA clearance for the acute treatment of pain associated with episodic cluster headache in adult patients through the utilization of a mild electrical stimulation to the vagus nerve that passes through the skin.²⁰ In January 2018, gammaCore received FDA clearance for the acute treatment of pain associated with migraine in adult patients, making it the first non-invasive, handheld medical therapy applied at the neck that acutely treats the pain associated with episodic cluster headache and migraine in adult patients.²⁰

The FDA clearance of gammaCore was supported by the results of the PRESTO trial, in which acute treatment with gammaCore demonstrated superiority over sham for pain freedom at 30, 60, and 120 minutes; and treatment with nVNS

led to significantly higher pain-free rates compared to sham for the first treated migraine attack at 30 minutes (12.7% vs. 4.2%, respectively, $P=0.012$) and at 60 minutes (21.0% vs. 10.0%, respectively, $P=0.023$).²¹ The manufacturer expects commercial availability of gammaCore

for the acute treatment of pain associated with migraine headache in adults in the second quarter of 2018.²⁰

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gammaCore® (non-invasive vagus nerve stimulator) is indicated for the acute treatment of pain associated with episodic cluster headache and migraine headache in adult patients

- The safety and effectiveness of gammaCore (nVNS) have not been established in the acute treatment of chronic cluster headache
- gammaCore has not been shown to be effective for the prophylactic treatment of migraine headache, chronic cluster headache, or episodic cluster headache
- The long-term effects of the chronic use of gammaCore have not been evaluated
- Safety and efficacy of gammaCore have not been evaluated in the following patients, and therefore it is NOT indicated for:
 - Patients with an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
 - Patients diagnosed with narrowing of the arteries (carotid atherosclerosis)
 - Patients who have had surgery to cut the vagus nerve in the neck (cervical vagotomy)
 - Pediatric patients
 - Pregnant women
 - Patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia
- Patients should not use gammaCore if they:
 - Have a metallic device such as a stent, bone plate, or bone screw implanted at or near their neck
 - Are using another device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device (e.g., mobile phone)

Note: This list is not all inclusive. Please refer to the gammaCore Instructions for Use for all of the important warnings and precautions before using or prescribing this product.

Available by prescription only. US Federal Law restricts this device to sale by or on the order of a licensed healthcare provider.

Reference: 1. gammaCore Instructions for Use. Basking Ridge, NJ: electroCore, LLC; 2018.



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Uterine Fibroids:

Current Treatment Options and Pipeline Update

Background

Uterine fibroids, or leiomyomas, are benign tumors of the uterus that most women will develop during their reproductive years.¹ With 400,000 new cases per year and an estimated 26 million women in the U.S. affected, they are the most common reproductive tumor in women.¹⁻⁶ Uterine fibroids can be symptomatic or asymptomatic, but more than 15 million women will experience symptoms or health concerns from this condition.^{7,8}



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While these fibroids are noncancerous and do not increase the risk of uterine cancer, associated symptoms can have a large impact on patients' quality of life, with symptoms including heavy bleeding, prolonged menstrual cycles, infertility, and pelvic pressure and pain, among others.⁹

Economic Impact and Need for New Treatments

There is limited published information on the economic impact of uterine fibroids on patients, but research suggests there is an estimated direct cost of \$4 billion to the U.S. economy.¹⁰ Additional research has suggested that direct and indirect costs range from \$11,000 to \$25,000 per patient per year after diagnosis or surgery.¹¹ Effective medical and surgical treatments are

available; however, these treatments are costly and associated with various drawbacks. Currently available prescription therapies are associated with unwanted side effects that prove problematic for many patients, and surgical treatments are invasive and can impact patients' fertility. Surgical management is also associated with high indirect costs for recovery time, which research suggests can result in an additional \$44,172 in one year after a hysterectomy in the U.S.¹⁰ For women with uterine fibroids, there is a large unmet need for clinically effective and cost-effective treatments with improved safety and tolerability profiles that seek to not only manage symptoms, but also shrink the tumor size and address associated health concerns.⁹

Treatment Options

Treatment is generally initiated only in patients who are symptomatic.² Uterine fibroid management can be achieved through medical therapy, surgery, or interventional radiology. Medical therapy may involve hormonal treatments or antifibrinolytic agents.¹² Surgical treatments include endometrial ablation, myomectomy, and hysterectomy.^{12,13} Interventional radiology options include uterine artery embolization (UAE) or uterine artery occlusion, high-intensity focused ultrasound (HIFU) for fibroid ablation, and radiofrequency fibroid ablation.^{12,13} These

options will be explored in greater detail in Figures 1 and 2.

Hormonal Therapies

Various hormonal therapies are available for the treatment of uterine fibroids. Such treatments include gonadotropin-releasing hormone (GnRH) agonists, progesterone receptor agents, and estrogen receptor agents and combined hormonal therapy.¹³

GNRH AGONISTS

Three GnRH agonists are available in the U.S. These include leuprolide acetate depot (injectable), goserelin (injectable), and nafarelin acetate (nasal spray). GnRH agonists reduce fibroid and overall uterus size as well as bleeding; however, these agents are associated with the onset of menopausal symptoms as well as lipid profile changes and bone loss.¹³

PROGESTERONE RECEPTOR AGENTS

Currently available medications that work through progesterone pathways include mifepristone and levonorgestrel-releasing intrauterine devices (IUDs).¹³ Mifepristone reduces fibroid size and overall uterine volume.¹³ The results of a small but poor-quality study suggested that the use of a levonorgestrel-containing IUD may improve bleeding; however, there is insufficient evidence to support the effectiveness of the IUD in reducing bleeding and fibroid size.¹³

ESTROGEN RECEPTOR AGENTS AND COMBINED HORMONAL THERAPY

In clinical studies, estrogen receptor agents were found to offer no or small decreases in fibroid size and no improvement in bleeding in premenopausal women; combined hormonal replacement therapy also did not offer changes in fibroid size.¹³

Antifibrinolytic Therapy

In a pooled analysis of data from two independent trials, statistically significant reductions in menstrual blood loss (MBL) volume were observed at treatment cycle three with tranexamic acid compared with placebo ($P<0.001$).¹³

FIGURE 1. SURGICAL INTERVENTIONS

Procedure	Description of Effectiveness*
Endometrial ablation	There is insufficient evidence to evaluate the effectiveness of endometrial ablation in improving symptoms. ¹³
Myomectomy	There is insufficient evidence to evaluate the effectiveness of myomectomy in reducing bleeding, and there is a risk of fibroid recurrence with this procedure. ¹³
Hysterectomy	The strength of evidence for improved quality of life following hysterectomy is low. ¹³

FIGURE 2. INTERVENTIONAL RADIOLOGY

Procedure	Description of Effectiveness*
UAE or uterine artery occlusion	There is high strength of evidence to support the effectiveness of UAE for reducing fibroid volume and moderate strength of evidence to support its improvements in bleeding and quality of life. ¹³ There is insufficient evidence to determine the effects of UAE on reproductive outcomes. ¹³ Insufficient evidence exists to determine the effectiveness of uterine artery occlusion. ¹³
HIFU	There is low strength of evidence to support that HIFU reduces fibroid and uterine size, and there are insufficient patient-reported outcomes. ¹³
Radiofrequency fibroid ablation	Two small poor-quality studies have been completed, and the results of the planned five-year follow-up study are not yet available to evaluate long-term outcomes. ¹³

Abbreviations: HIFU = high-intensity focused ultrasound; UAE = uterine artery embolization

*The majority of these studies do not have follow-up patient outcomes (e.g. change in bleeding, fibroid-related pain, etc.) beyond the postoperative period.

The most common adverse effects associated with tranexamic acid include headache; migraine; fatigue; anemia; bone, joint, or muscle pain; and back, stomach, and sinus pain.¹⁴

Treatment Pipeline

ULIPRISTAL ACETATE

Ulipristal acetate (UPA) is a selective progesterone receptor modulator that is currently being studied for

the treatment of uterine fibroids. This agent, which is currently only available as a single 30 mg dose in the U.S., is more commonly recognized for its use in the emergency contraception setting. UPA (Allergan) is currently being studied in a 5 mg daily dose form for uterine fibroid management.

In two randomized trials, UPA once daily was compared to placebo and to leuprolide acetate.^{15,16} In the first trial

With 400,000 new cases per year and an estimated 26 million women in the U.S. affected, uterine fibroids are the most common reproductive tumor in women.

(N=242) in women with heavy menstrual bleeding, fibroid-associated anemia, and a uterus that was ≤ 16 weeks gestation size, treatment with once daily UPA 5 mg and 10 mg resulted in a higher rate of resolution of menorrhagia compared to placebo (91% and 92% vs. 19%, respectively) and a slightly higher increase in hemoglobin (4.3 g/dL and 4.2 g/dL vs. 3.1 g/dL, respectively).¹⁵ Significant reductions in fibroid volume were observed in both UPA dosing arms compared to placebo (-21% volume for 5 mg dose and -12% for 10 mg dose vs. +3% for placebo).¹⁵

In the second trial (N=307) in women with menorrhagia and a uterus that was ≤ 16 weeks gestation size, treatment with once daily UPA 5 mg and 10 mg resulted in comparable rates of menorrhagia resolution versus leuprolide acetate 3.75 mg monthly, but resolution was achieved more quickly in the UPA groups (approximately 6 days vs. 30 days, respectively).¹⁶ Additionally, a lower frequency of severe hot flashes was observed in the UPA 5 mg and 10 mg groups compared to the leuprolide acetate group (11% and 10% vs. 40%, respectively).¹⁶ The uterine size reduction was lower in the UPA 5 mg and 10 mg groups compared to the leuprolide acetate group (20% and 22% vs. 47%, respectively).¹⁶

In patients who received a three-month course of UPA, more than 90% of patients experienced controlled uterine bleeding, with shorter median times to control bleeding in the UPA group compared to the leuprolide acetate group (5 to 7 days vs. 21 days, respectively).^{15,16} Treatment with UPA was also observed to have a sustained effect (up to 6 months) in fibroid shrinkage in patients who did not undergo surgery after the three-month study period compared to the rapid fibroid regrowth experienced

by patients in the leuprolide acetate group; patients in the leuprolide acetate group experienced fibroid sizes reaching pre-therapy dimensions by six months post-treatment.^{15,16}

In clinical trials, the safety profile of UPA during multiple treatment courses has been well-documented.¹⁵⁻¹⁷ Most side effects were mild or moderate in severity, with headaches and hot flashes as the most commonly reported adverse effects; of note, the frequency of these events decreased with each additional treatment course.¹⁷

In October 2017, the manufacturer announced that the U.S. Food and Drug Administration accepted the new drug application (NDA) for UPA and expects a Prescription Drug User Fee Act (PDUFA) action date in the first half of 2018.¹⁸

ELAGOLIX

Elagolix (AbbVie, Neurocrine Biosciences) is an oral, non-peptide gonadotropin-releasing hormone (GnRH) receptor inhibitor that is being developed as an alternative to injectable GnRH antagonists for the treatment of uterine fibroids and endometriosis.¹⁹ In a phase IIb study (N=567) of premenopausal women with and without hormone add-back for the treatment of uterine fibroids, the study met its composite primary endpoint by achieving an MBL volume of <80 mL as well as $\geq 50\%$ reduction in MBL volume from baseline to month six ($P<0.001$).¹⁹ There are two ongoing replicate phase III trials evaluating the safety and efficacy of elagolix plus estradiol-norethindrone acetate for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. Data from a six-month interim analysis of the first of two replicate phase III studies were released in February. The

ELARIS UF-I study met its primary endpoint and results demonstrated that at month six, treatment with elagolix plus low-dose add-back therapy reduced heavy menstrual bleeding, with 68.5% of women in the active treatment group achieving clinical response compared to 8.7% of patients in the placebo group ($P<0.001$).²⁰ Patients in the study will continue with post-treatment follow-up or participate in a blinded six-month extension study.

Positive results from ELARIS UF-II — the second replicate study — were recently announced as well. At month six, treatment with elagolix 300 mg twice daily in combination with low-dose hormone therapy reduced heavy menstrual bleeding, with 76.2% of women with uterine fibroids achieving clinical response compared to 10.1% of patients in the placebo group ($P<0.001$).²¹ Clinical response was defined as MBL volume of <80 mL during month six and a 50% or greater reduction in MBL volume from baseline to month six.²¹ The study met all secondary endpoints at month six ($P<0.02$).²¹

Pending positive results of these trials, the manufacturer may submit a supplemental NDA for the approval of elagolix in the treatment of uterine fibroids in 2019.²² Currently, elagolix has a PDUFA date of May 2018 for the treatment of endometriosis with associated pain.²³

Conclusion

There is a large unmet need for effective treatments with improved safety and tolerability profiles for patients with uterine fibroids. The treatment selection process currently involves an evaluation of the severity of symptoms, age, infertility, desire to preserve the uterus, and uterine fibroid classification.⁹ Existing medical therapies and surgical treatments are associated with a number of concerns, including, but not limited to, cost, undesirable adverse effects, negative impact on fertility, and/or varying levels of invasiveness. Surgery remains an appropriate treatment option for some patients; however, a nonsurgical alternative in the form of medical therapy that could

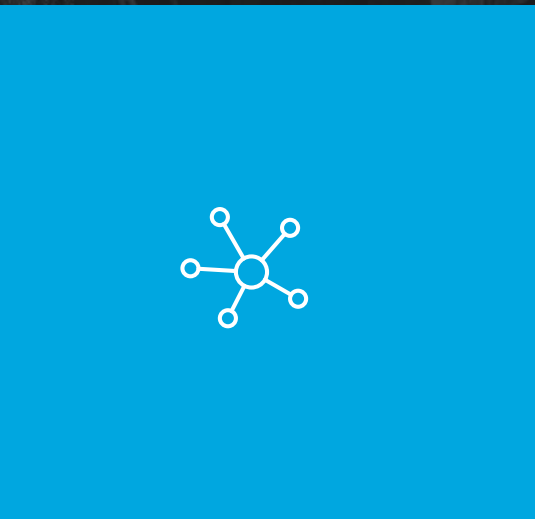
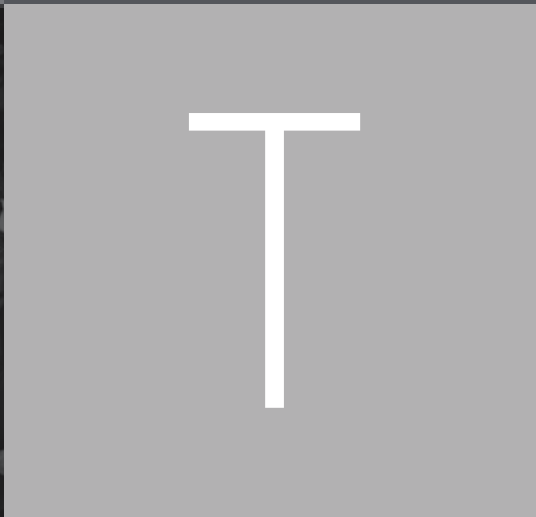
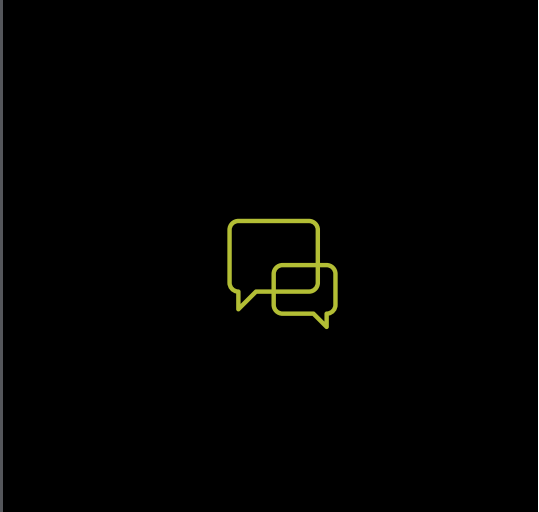
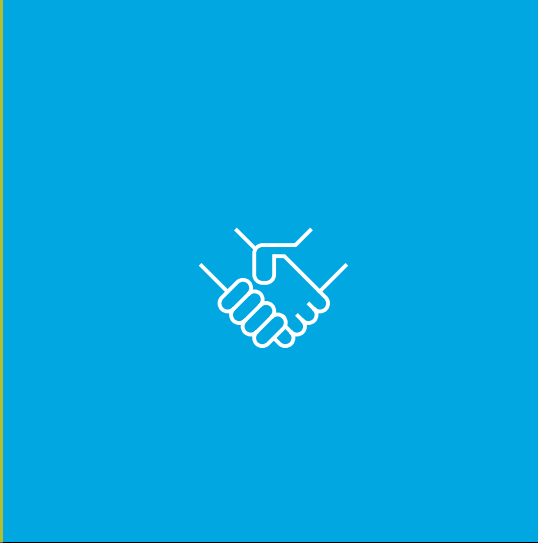
allow for less invasive surgery or avoidance of surgery altogether represents an attractive option for this patient group.⁹ If approved, UPA may potentially be restricted to only patients who are surgical candidates and have a restricted number of acceptable cycles patients can receive.²⁴ Despite potential labeling

restrictions, the potential approval of UPA could make this investigational therapy the first oral therapy that is safe and effective for the treatment of uterine fibroids.²⁴ Payors are encouraged to keep a watchful eye on this potentially transformative therapy as it approaches its anticipated PDUFA date time frame to

prepare for a possible paradigm shift in uterine fibroid management.

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Schizophrenia:

Characteristics and Health Resource Utilization Among Medicaid Superutilizers

Researchers have reported that a small group of patients accounts for a very large proportion of healthcare resource utilization (HRU).¹ In the U.S., approximately 22% of total annual healthcare expenses is incurred by just 1% of the population.^{2,3}

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Among Medicaid beneficiaries, however, the magnitude of disparity in healthcare spending is even greater; approximately 1% of Medicaid beneficiaries incurs 25% of Medicaid expenditures, and 5% of Medicaid beneficiaries account for 54% of Medicaid expenditures.⁴ The term “superutilizers” describes a small group of individuals who consume a disproportionately large share of healthcare resources.¹ One major reason for the larger healthcare expenses incurred by superutilizers is the presence of multiple comorbidities in this group. The top 1% of individuals responsible for nearly a quarter of annual healthcare expenses has at least three chronic conditions, and more than 60% of this group has five or more chronic conditions.²

Superutilizers incur larger healthcare expenses not only as a result of their multiple comorbidities, but also potentially due to a lack of coordinated care, preventive care, or care in the most appropriate settings.² Research has found that superutilizers are more likely to have poor physical and mental

health, no usual source of care, and higher-than-average utilization of other healthcare services.⁵ Additionally, Healthcare Cost and Utilization Project (HCUP) researchers reported that superutilizers had an average of four times as many hospital stays per year, an average all-cause 30-day readmission rate that was four to eight times greater, longer hospital stays, and higher average hospital costs compared to other patients.¹

To address the underlying needs of superutilizers, state Medicaid programs and other provider groups have begun implementing programs designed to better coordinate care and curb healthcare costs.² Not all programs have been successful as many have only addressed surface issues and have missed underlying concerns, such as lack of transportation and financial challenges for patients and inadequate financial and staffing resources for providers.⁶

Clinically appropriate interventions designed to address both surface and underlying issues in this population can result in better patient care and cost savings for the health plan or healthcare system.⁷ Appropriate patient selection helps to ensure that any program implemented makes the biggest impact upon the patient population of interest. Identification of superutilizers may be an effective way of prioritizing patients who may benefit from more targeted or intensive care or support.

HCUP researchers reported that schizophrenia is among the top 10 principal diagnoses for superutilizers (defined as patients with at least four hospital stays during the study period) under 65 years of age who were covered by Medicare, Medicaid, or private insurance.¹ In fact, schizophrenia was the second most common diagnosis reported for superutilizers. Further, a significant cost driver for Medicaid patients with schizophrenia was the use of inpatient services, with 28% and 31% of hospital stays being attributed to Medicaid and Medicare patients, respectively.^{1,7,8}

Schizophrenia is a chronic, debilitating disease that poses significant burdens on patients and their caregivers.⁹ Schizophrenia has been long recognized as difficult and costly to treat; unsuccessful treatment often results in schizophrenia patients having difficulty in reaching full attainment of personal goals (e.g. education, career, relationships).^{10,11} The incidence of schizophrenia is low (15.2 per 100,000 person-years); however, the prevalence is high due to the chronic nature of the disease (4.6 per 1,000 persons).¹² Patients diagnosed with schizophrenia often experience relapses characterized as periods of psychosis, costly emergency room visits, and hospitalizations; patients with prior relapse have been shown to incur three times the cost of those without prior relapse.⁸ Due to direct and indirect

costs, relapses are financially draining to schizophrenia patients and health-care systems globally. In a 2010 report, approximately 67% of U.S. schizophrenia patients reported healthcare coverage by Medicaid.¹³ Among community-dwelling Medicaid schizophrenia patients, the annual economic burden of mental health-related costs is estimated to be \$11,700 per patient.¹⁴ Frequent inpatient admissions are undoubtedly an issue in the Medicaid schizophrenia population.

The purpose of this study was to examine and describe patient and treatment characteristics of Medicaid superutilizers diagnosed with schizophrenia compared to those of non-superutilizers with schizophrenia in a statewide managed Medicaid plan.

Methods
DATA SOURCES

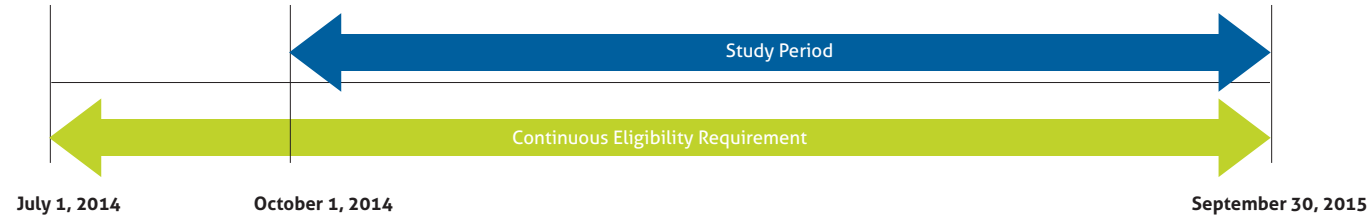
Data was drawn from Magellan Health Services' administrative claims database for patients enrolled in a managed Medicaid plan. Magellan collects and processes all ambulatory, outpatient/professional, pharmacy, and institutional claims for patients in this plan. The database has pharmacy and medical administrative claims for more than 50,000 patients with severe mental illness. Data from a single statewide managed Medicaid plan were extracted for analysis.

STUDY DESIGN AND POPULATION

This was a retrospective 12-month cross-sectional study of Medicaid claims data from October 1, 2014 to September 30, 2015. Inclusion criteria consisted of continuous enrollment in the plan with both medical and pharmacy benefits from July 1, 2014 to September 30, 2015 (see Figure 1); at least two paid pharmacy claims for an oral or long-acting injectable (LAI) typical or atypical antipsychotic medication indicated for chronic use during the study period; and at least one diagnosis of schizophrenia (ICD-9 codes 295.xx) in any position on an inpatient claim or in any position on two outpatient claims during the study period. Patients were excluded if they were younger than 18 years old at the beginning of the study period or if they had dual Medicare-Medicaid enrollment at any time during the study period. Qualifying patients were classified into two cohorts based on the number of inpatient hospital admissions during the study period. The superutilizer group consisted of all patients with four or more inpatient hospitalizations, consistent with Jiang et al; all other patients were classified as non-superutilizers.¹ Patient characteristics analyzed included age, gender, and physical and behavioral health comorbidities. HRU analyzed in this study included number of inpatient admissions, length of stay, number of inpatient days, number of

FIGURE 1. STUDY PERIOD

Figure 1 displays the 12-month study period and continuous eligibility requirement. Patients' demographics and health resources utilized were evaluated during the 12-month study period. As an eligibility requirement, patients were required to have continuous Medicaid enrollment at least three months prior to and during the study period.



emergency department (ED) visits, and medication use. For study purposes, ED visits that resulted in admissions were counted as inpatient visits; all other visits were counted as ED visits.

STATISTICAL ANALYSIS

Descriptive statistics are represented with the mean (standard deviation [SD]) reported for continuous variables and proportions reported for categorical variables. Statistical comparisons between groups were conducted using two-sided Student's t-tests for continuous variables and chi-square tests for categorical variables.

Results

DEMOGRAPHICS

A total of 2,273 patients met the inclusion criteria. Figure 2 summarizes the distribution of inpatient admissions within the entire study sample. Nearly half of all patients had no hospitalizations during the 12-month study period, and 419 (18.4%) were classified as superutilizers. Superutilizers and non-superutilizers did not differ

significantly in mean age or age distribution, and both groups were predominantly male, although a significantly higher proportion of superutilizers were male compared to non-superutilizers (64.9% vs. 55.4%, $P<0.001$). Table 1 displays demographic characteristics of the study population.

CLINICAL CHARACTERISTICS

Table 2 presents medical and psychiatric comorbid conditions in the study population. Superutilizers had more comorbid psychiatric conditions, including substance-related disorders, than non-superutilizers (74.7% vs. 25.6%, $P<0.001$).

Superutilizers had a higher mean Charlson Comorbidity Index (CCI) score than non-superutilizers (2.2 vs 0.6, $P<0.001$), and a larger proportion of superutilizers had comorbid physical health conditions such as cardiovascular disease and chronic pulmonary disease than non-superutilizers (69.7% vs. 30.7% and 43.9% vs. 10.0%, respectively).

HEALTHCARE RESOURCE UTILIZATION

Table 3 describes HRU in the study population. Superutilizers averaged more inpatient days (39.47 days [median 32] vs. 8.07 days [median 6] for non-superutilizers, $P<0.001$). Moreover, the mean length of stay per admission for superutilizers was over more than twice that of non-superutilizers (5.48 days vs. 2.54 days, $P<0.001$). The distribution of hospitalizations was skewed, with nearly half of superutilizers having seven or more hospitalizations (46.8%). Similarly, the distribution of hospitalizations among non-superutilizers was skewed, with the majority (59.9%) having no hospitalizations. Additionally, a higher proportion of superutilizers had one or more ED visits compared to non-superutilizers (55.9% vs. 15.9%, respectively, $P=0.009$; see Table 3).

MEDICATION UTILIZATION

On average, superutilizers received a greater number of unique antipsychotics during the study period. Treatment with LAI antipsychotics did not differ significantly between the superutilizer

FIGURE 2. NUMBER OF INPATIENT ADMISSIONS FOR THE 12-MONTH STUDY PERIOD

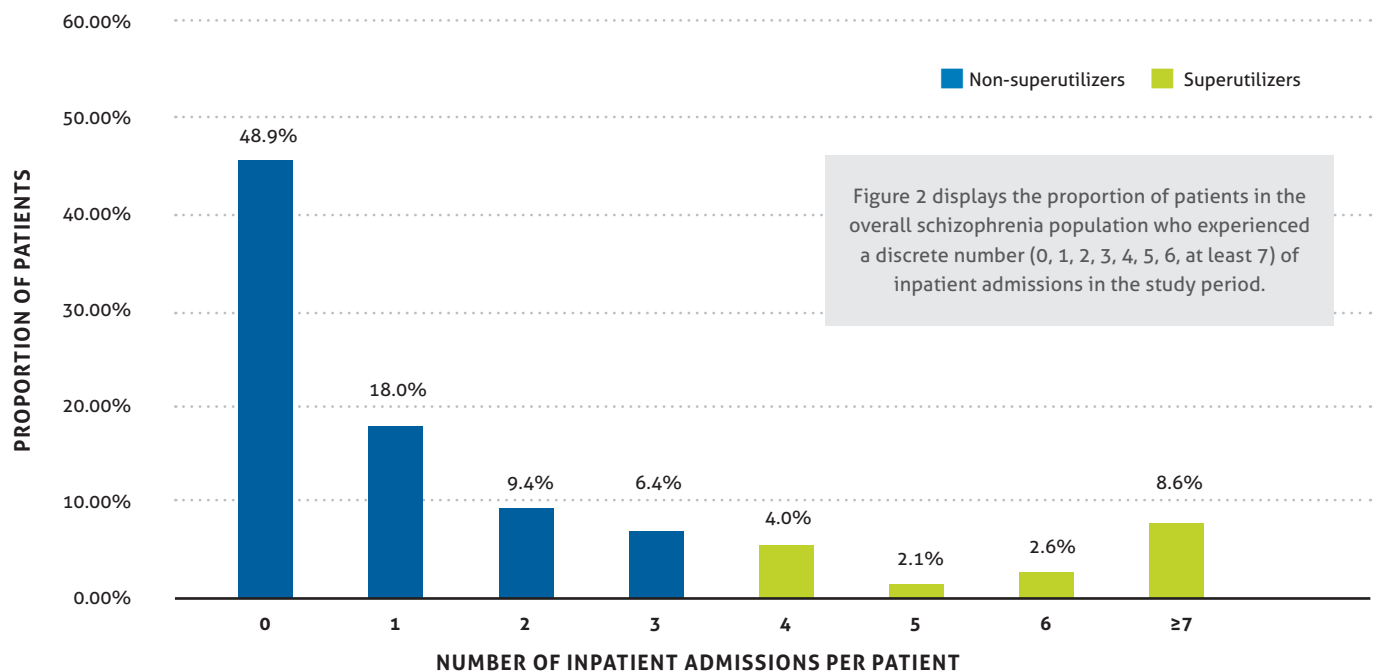


TABLE 1. DEMOGRAPHICS

Trait	Overall (N=2,273)		Non-superutilizers (N=1,854)		Superutilizers (N=419)		p value ^a
Percentage, %	100%		81.6%		18.4% (2.69) [1.00]		<0.0011
Age category, n (%)							
18-25	331	14.6%	272	14.7%	59	14.1%	0.519
26-34	475	20.9%	379	20.4%	96	22.9%	
35-44	391	17.2%	315	17.0%	76	18.1%	
45-54	582	25.6%	489	26.4%	93	22.2%	
>55	494	21.7%	399	21.5%	95	22.7%	
Sex, n (%)							
Female	974	42.9%	827	44.6%	147	35.1%	<0.001
Male	1,299	57.1%	1,027	55.4%	272	64.9%	

^ap-value is the result of the Chi-square test between superutilizers and nonsuperutilizers.

and non-superutilizer cohorts (7.2% and 8.9%, respectively; see Table 4).

Discussion

This analysis provides additional insights into a subpopulation of Medicaid patients that accounts for a disproportional share of HRU and is the first to describe this phenomenon in a schizophrenia population. Superutilizers comprised less than 20% of the included population yet accounted for 63% of all inpatient admissions. Moreover, a subset of nearly half of superutilizers (46.8%) was hospitalized seven or more times in one year, suggesting that further refinement of the definition could identify a more targeted population with even greater needs. Further research on classifying superutilizers within different diagnostic categories may enable population health decision-makers to more efficiently manage care for subpopulations with substantial unmet needs. The significantly higher rate of physical and mental comorbidities seen in superutilizers and exposure to a greater number of unique antipsychotics compared to non-superutilizers suggest that these

patients are more complex clinically and may be less responsive and/or less adherent to prescribed treatment regimens. One striking finding is that similar proportions of superutilizers and non-superutilizers received LAI antipsychotics. While schizophrenia treatment guidelines recommend the use of LAI antipsychotics in patients who prefer them, experience multiple relapses, or struggle with adherence to daily oral antipsychotics, our findings suggest that clinicians are not following these guidelines, even for schizophrenia superutilizers.¹⁵ There may be several reasons for this, including reluctance to offer LAIs to their patients or lack of awareness of their patients' unmet needs.

A number of approaches addressing the needs characteristic of this population have demonstrated the potential for reducing hospitalization. The complexity of superutilizers, as evidenced by their higher prevalence of medical and psychiatric comorbidities in superutilizers, suggests that targeted care management may help meet their multiple underlying needs. Patient-centered medical homes (PCMH) may offer an opportunity to

integrate physical and mental health in the context of primary care, though this may also meet the specialized needs of patients with schizophrenia.¹⁶

Incomplete adherence to oral antipsychotics is a common and prominent risk factor for increased psychiatric hospitalization in patients with schizophrenia; a gap of just 10 days can double the risk of hospitalization.^{17,18} Programs such as assertive community treatment (ACT) are designed to reduce recidivism among persons with serious mental illness and combine psychosocial outreach with medication management. Telephonic outreach management may also help reduce recidivism in high-risk populations by providing ongoing reminder calls and appointment verification, in addition to utilizing staff who can detect signs and symptoms of impending relapse.¹⁹ However, the utility of telephonic outreach in a subset of Medicaid superutilizers with schizophrenia may not be feasible if they have unstable living conditions that are in part the consequence of their recurrent illness.

LAI antipsychotics administered every two to 12 weeks may reduce the burden

TABLE 2. CLINICAL CONDITIONS

Clinical Conditions	Overall (N= 2,273)		Non-superutilizers (N=1,854)		Superutilizers (N=419)		p value ^b
Mean CCI ^a (SD) [median]	0.91	(1.73) [0.00]	0.6	(1.25) [0.00]	2.23	(2.69) [1.00]	<0.0011
CCI, n (%)							
0	1,386	61.0%	1,270	68.5%	116	27.7%	<0.001
1	462	20.3%	352	19.0%	110	26.3%	
2	182	8.0%	120	6.5%	62	14.8%	
>3	243	10.7%	112	6.0%	131	31.3%	
Schizophrenia diagnosis, n (%)							
Schizophrenia	2,273	100.0%					
Schizoaffective	916	40.2%	608	32.8%	308	73.5%	<0.001
Comorbid mental health conditions, n (%)							
Bipolar and related mood disorders	1,034	45.5%	731	39.4%	303	72.3%	<0.001
Depressive disorders	966	42.5%	625	33.7%	341	81.4%	<0.001
Anxiety disorders	722	31.8%	436	23.5%	286	68.3%	<0.001
Substance-related and addictive disorders	787	34.6%	474	25.6%	313	74.7%	<0.001
Personality disorders	153	6.7%	63	3.4%	90	21.5%	<0.001
Comorbid physical health conditions, n (%)							
Cardiovascular disease	862	37.9%	570	30.7%	292	69.7%	<0.001
Pulmonary disease	339	14.9%	185	10.0%	184	43.9%	<0.001
Diabetes	445	19.6%	314	16.9%	131	31.3%	<0.001
Liver disease	262	11.5%	159	8.6%	103	24.6%	<0.001
HIV and AIDS	42	1.8%	20	1.1%	22	5.3%	<0.001

^aCCI = Charlson Comorbidity Index^bp-value is the result of Chi-square or t-test between superutilizers and nonsuperutilizers.

of adherence to oral antipsychotics for patients, with associated reduced hospitalizations.^{20,21} Our finding that LAI antipsychotics were prescribed in less than 10% of superutilizers suggests that clinicians may not be making treatment decisions based on existing evidence to reduce potentially avoidable hospitalizations. Non-evidence-based practices for antipsychotic prescribing

have been well-documented in the literature. In one study, a statewide quality improvement program successfully reduced antipsychotic polypharmacy by notifying physicians of patients in their practice receiving antipsychotic polypharmacy and recommending a review of their medication regimen.²² It is possible that a similar intervention helping clinicians identify superutilizers

with schizophrenia in their practice may prompt a treatment plan review that includes a consideration of LAI antipsychotic therapy.

LIMITATIONS

This study has several limitations, including the cross-sectional design, which precludes inferences of causality. Due to the limited data elements

available through administrative claims data, researchers were unable to account for potentially confounding effects of unobserved factors, such as living situation, patient support programs, or assertive community treatment. Further, the claims analyzed in this research were generated for administrative purposes, and thus there is potential for coding bias or other confounding associated with their original purpose. The results observed from a one-year study period cannot be easily extrapolated to longer follow-up periods. Finally, this study was conducted on claims from a single state's Medicaid population; therefore, the results may not be representative of Medicaid populations in other states.

Future research is warranted to further characterize superutilizers with schizophrenia, including the longitudinal durability of high utilization (i.e., Do superutilizers continue their high rates of recidivism?). Predictors of superutilizer status may enable preventive interventions, such as case management and LAI antipsychotic use to prevent or delay hospitalizations. Finally, among identified superutilizers, evaluating the impact of case management and LAI antipsychotic use will enable population health decision-makers to make informed choices on how to most efficiently manage the outcomes of schizophrenia patients with high unmet needs.

CONCLUSION

As in other populations, a small subset of Medicaid patients with schizophrenia account for a disproportionately large share of inpatient admissions and ED visits. This superutilizer population appears to be more complex medically and psychiatrically than non-superutilizers but not more likely to receive LAI antipsychotics. Effective identification of and engagement with this population and activation of treatment teams may improve patient outcomes and reduce avoidable costs.

TABLE 3. INPATIENT ADMISSION AND EMERGENCY DEPARTMENT METRICS

Health Resource Utilization	Overall (N= 2,273)		Non-superutilizers (N=1,854)		Superutilizers (N=419)		p value ^a
Inpatient admissions							
>1 visit n (%)	743	36.2%	342	18.4%	419	100%	<0.001
Number of admissions, mean (SD) [median]	2.11	(3.22) [1.00]	0.75	(0.96) [0.00]	7.21	(3.60) [6.00]	
Length of stay per admission, mean (SD) [median]	4.21	(5.75) [3.00]	2.54	(4.22) [1.00]	5.48	(6.40) [4.00]	<0.001
Number of inpatient days per patient, mean (SD) [median]	9.84	(19.10) [1.00]	8.07	(7.95) [6.00]	39.47	(26.94) [32.00]	<0.001
Number of inpatient admissions per patient, n (%)							
0	1,111	48.9%	1,111	59.9%			<0.001
1	410	18.0%	401	21.6%			
2	213	9.4%	221	11.9%			
3	146	6.4%	121	6.5%			
4	90	4.0%			116	27.7%	
5	48	2.1%			48	11.5%	
6	59	2.6%			59	14.1%	
≥7	196	8.6%			196	46.8%	
Emergency department visits							
Patients with ≥1 visit, n (%)	528	23.2%	294	15.9%	234	55.9%	0.009
>1 visit, n (%)	191	8.4%	76	4.1%	115	27.5%	<0.001

^ap-value is the result of Chi-square or t-test between superutilizers and nonsuperutilizers.

TABLE 4. MEDICATION UTILIZATION

Medication Utilization	Overall (N= 2,273)		Non-superutilizers (N=1,854)		Superutilizers (N=419)		p value ^a
Antipsychotic (APS) medication exposure							
Number of unique APS dispensed, mean (SD) [median]	1.61	(0.91) [1.00]	1.48	(0.76) [1.00]	2.25	(1.23) [2.00]	<0.001
Rx for any long-acting injectable	195	7.4%	165	8.9%	30	7.2%	0.251

^ap-value is the result of Chi-square or t-test between superutilizers and nonsuperutilizers.

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Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
andexanet alfa (AndexXa®)	Portola Pharmaceuticals Inc.	Anticoagulant reversal agent	IV	Breakthrough therapy; orphan drug	5/4/18
elagolix	AbbVie Inc., Neurocrine Biosciences Inc.	Endometriosis	Oral	Priority review	5/4/18
erenumab (Aimovig™)	Amgen Inc.	Migraine prevention	SC	Submitted	5/17/18
avatrombopag	Dova Pharmaceuticals Inc.	Thrombocytopenia in CLD	Oral	Priority review	5/21/18
lenvatinib (Lenvima®)	Eisai Inc.	Advanced HCC	Oral	Orphan drug	5/24/18
certolizumab pegol (Cimzia®)	UCB Inc.	Psoriasis	SC	Submitted	5/25/18
pegvaliase (PEG-PAL)	BioMarin Pharmaceutical Inc.	PKU	SC	Orphan drug; priority review	5/25/18
baricitinib	Eli Lilly and Company	RA	Oral	Submitted	June, 2018
tofacitinib citrate (Xeljanz®/Xeljanz XR®)	Pfizer Inc.	UC	Oral	Submitted	June, 2018
mogamulizumab	Kyowa Hakko Kirin Co. Ltd.	CTCL	IV	Breakthrough therapy; orphan drug; priority review	6/4/18
fremanezumab	Teva Pharmaceutical Industries Ltd.	Migraine	IV, SC	Priority review	6/15/18
halobetasol propionate/tazarotene (Duobrii)	Valeant Pharmaceuticals International Inc.	Plaque psoriasis	Topical	Submitted	6/18/18
cannabidiol (Epidiolex®)	GW Pharmaceuticals PLC	Dravet syndrome; LGS	Oral	Fast track; orphan drug; priority review; rare pediatric disease	6/27/18
aripiprazole lauroxil NanoCrystal® Dispersion (ALNCD)	Alkermes PLC	Schizophrenia	Oral	Submitted	6/30/18
binimetinib and encorafenib	Array BioPharma Inc.	Melanoma	Oral	Submitted	6/30/18
buprenorphine spray	INSYS Therapeutics Inc.	Moderate-to-severe acute pain	SL/oral transmucosal	Submitted	7/28/18
risperidone monthly depot (RBP-7000)	Indivior PLC	Schizophrenia	SC	Submitted	7/28/18
lorlatinib	Pfizer Inc.	NSCLC	Oral	Breakthrough therapy; orphan drug	August, 2018
lofexidine hydrochloride	US WorldMeds LLC	Symptom management during opioid withdrawal	Oral	Fast track; priority review	Q2, 2018

Abbreviations: CLD = chronic liver disease; CTCL = cutaneous T-cell lymphoma; FDA = Food and Drug Administration; HCC = hepatocellular carcinoma; IV = intravenous; LGS = Lennox-Gastaut syndrome; NSCLC = non-small cell lung cancer; PKU = phenylketonuria; Q2 = second quarter; RA = rheumatoid arthritis; SQ = subcutaneous; SL = sublingual; UC = ulcerative colitis



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Long-Acting Buprenorphine Injectable

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In November 2017, the Food and Drug Administration (FDA) approved Sublocade (buprenorphine extended-release), the first subcutaneous (SQ), once-monthly injectable depot buprenorphine.¹ Sublocade (Indivior PLC) is indicated for the treatment of moderate-to-severe opioid use disorder (OUD) in adults on a stable dose of a transmucosal buprenorphine-containing product for ≥ 7 days.¹ The FDA granted Sublocade priority review and fast track designations.¹

The safety and efficacy of Sublocade were established in clinical studies including 848 adults with a diagnosis of moderate-to-severe OUD.¹ After stabilization on buprenorphine/naloxone sublingual film, patients were switched to monthly doses of Sublocade or placebo.¹ Urine drug screening and self-reported illicit opioid use during the six-month treatment period measured response.¹ Sublocade-treated patients had more weeks without positive urine tests or self-reported opioid use; a higher proportion also had no evidence of illicit opioid use.¹ Common adverse effects with Sublocade included constipation, nausea, vomiting, and abnormal liver enzymes.¹

In clinical trials, the most common side effects from treatment

were constipation, nausea, vomiting, headache, drowsiness, injection site pain, itching at the injection site, and abnormal liver function tests.¹ While the panelists of the joint FDA advisory committee meeting voted 13-6 that the data support the safety of the 300 mg/100 mg high dose of the drug, many raised concerns about elevated liver enzymes in a patient group that is considered to be predisposed to hepatitis.²

Sublocade is a Schedule III controlled substance and should only be administered by a healthcare professional in conjunction with a complete treatment program that includes counseling and psychosocial support.¹ A boxed warning informs of the risks of IV self-administration; thus, it must be

prescribed and dispensed as part of a Risk Evaluation and Mitigation Strategy program to ensure that it is not distributed directly to patients.¹

Sublocade is available as 100 mg/0.5 mL and 300 mg/1.5 mL prefilled syringes. The starting dosage is 300 mg SQ monthly for two doses, followed by 100 mg monthly thereafter. Maintenance doses up to 300 mg monthly may be considered in select patients. The wholesale acquisition cost of Sublocade in the U.S. is \$1,580 per monthly dose for the 100 mg or 300 mg injection.

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2017 Medical Pharmacy Trend Report™ Key Findings

At Magellan Rx Management, we are committed to providing our clients with additional services that extend beyond our traditional pharmacy benefit manager core services. For this reason, we are proud to highlight in this issue the key findings of the eighth edition of the Medical Pharmacy Trend Report we published in 2018. The Medical Pharmacy Trend Report is the only detailed source analyzing medical benefit drug claims for benchmarks and trends, along with current medical benefit drug management approaches.

The report was developed with original guidance from our payer advisory board as well as reader feedback on our previous trend reports. This report includes a combination of primary and secondary research methodologies to deliver a comprehensive view of payer perceptions and health plan actions related to provider-administered infused or injected drugs paid under the medical benefit, also referred to as medical benefit drugs. The results of this study were a combination of findings from a survey of medical, pharmacy, and network directors at commercial health plans as well as medical benefit paid claims data across key lines of business (i.e., commercial and Medicare Advantage) and outpatient sites of service (i.e., physician offices, homes via home infusion, specialty pharmacies, and hospital outpatient facilities).

The key findings from the Medical Pharmacy Trend Report include the following:

- From 2015 to 2016, the annual per-member, per-month (PMPM) trend increased by 21% for commercial plans and 3% for Medicare plans, with PMPM costs of \$26.26 and \$46.97 for each plan type, respectively.
- The 2016 drug spend breakdown was 94% specialty and 6% non-specialty for commercial plans, with 10% of patients driving this spend, and 96% specialty and 4% non-specialty for Medicare plans, with 21% of patients driving this spend.
- For commercial plans, oncology and oncology support accounted for \$11.78 (45%) of the medical benefit drug PMPM spend; for Medicare plans, the same category accounted for \$28.05 (60%) of medical benefit drug PMPM spend.
- Eight of the top 20 commercial disease states or drug categories have more than doubled in PMPM spend between 2012 and 2016.
- Top 25 drugs represented 62% and 69% of total commercial and Medicare PMPMs, respectively.
- For commercial plans, member costs were 3%, while payer costs were 97%; for Medicare plans, member costs were 8% while payer costs were 92%.
- Innovative management strategies are being used by payers, with 62% of commercial payers reporting the use of dose optimization and 43% of payers reporting the use of vial rounding.
- Since 2012, there has been a 24% increase in the percentage of payers reporting using a site of service program, with 68% of payers now using this service.
- More than 94% of plans will be capturing, storing, and reporting national drug code information by 2019.

For instructions on downloading the Trend Report, please see the following page.

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PROFESSIONAL BRIEF SUMMARY
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WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with MAVYRET. HBV reactivation has been reported in HCV/HBV coinfectd patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfectd patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated [see Warnings and Precautions].

INDICATIONS AND USAGE

MAVYRET is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both.

CONTRAINDICATIONS

MAVYRET is contraindicated in patients with severe hepatic impairment (Child-Pugh C) [see Use in Specific Populations].

MAVYRET is contraindicated with atazanavir or rifampin [see Drug Interaction].

WARNINGS AND PRECAUTIONS

Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfectd patients who were undergoing or had completed treatment with HCV direct-acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure and death. Cases have been reported in patients who are HBSAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBSAg negative and anti-HBc positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients.

HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection reappearance of HBSAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increase in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBSAg and anti-HBc before initiating HCV treatment with MAVYRET. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with MAVYRET and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

Risk of Reduced Therapeutic Effect Due to Concomitant Use of MAVYRET with Carbamazepine, Efavirenz Containing Regimens, or St. John's Wort

Carbamazepine, efavirenz, and St. John's wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of MAVYRET. The use of these agents with MAVYRET is not recommended.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of MAVYRET cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Overall Adverse Reactions in HCV-Infected Adults Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

The adverse reactions data for MAVYRET in subjects without cirrhosis or with compensated cirrhosis (Child-Pugh A) were derived from nine Phase 2 and 3 trials which evaluated approximately 2,300 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV who received MAVYRET for 8, 12 or 16 weeks.

The overall proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.1% for subjects who received MAVYRET for 8, 12 or 16 weeks.

The most common adverse reactions, all grades, observed in greater than or equal to 5% of subjects receiving 8, 12, or 16 weeks of treatment with MAVYRET were headache (13%), fatigue (11%), and nausea (8%). In subjects receiving MAVYRET who experienced adverse reactions, 80% had an adverse reaction of mild severity (Grade 1). One subject experienced a serious adverse reaction.

Adverse reactions (type and severity) were similar for subjects receiving MAVYRET for 8, 12 or 16 weeks. The type and severity of adverse reactions in subjects with compensated cirrhosis (Child-Pugh A) were comparable to those seen in subjects without cirrhosis.

Adverse Reactions in HCV-Infected Adults treated with MAVYRET in Controlled Trials
ENDURANCE-2

Among 302 treatment-naïve or PRS treatment-experienced, HCV genotype 2 infected adults enrolled in ENDURANCE-2, adverse reactions (all intensity) occurring in at least 5% of subjects treated with MAVYRET for 12 weeks are presented in Table 1. In subjects treated with MAVYRET for 12 weeks, 32% reported an adverse reaction, of which 98% had adverse reactions of mild or moderate severity. No subjects treated with MAVYRET or placebo in ENDURANCE-2 permanently discontinued treatment due to an adverse drug reaction.

Table 1. Adverse Reactions Reported in ≥5% of Treatment-Naïve and PRS-Experienced Adults Without Cirrhosis Receiving MAVYRET for 12 Weeks in ENDURANCE-2

Adverse Reaction	MAVYRET 12 Weeks (N = 202) %	Placebo 12 Weeks (N = 100) %
Headache	9	6
Nausea	6	2
Diarrhea	5	2

ENDURANCE-3

Among 505 treatment-naïve, HCV genotype 3 infected adults without cirrhosis enrolled in ENDURANCE-3, adverse reactions (all intensity) occurring in at least 5% of subjects treated with MAVYRET for 8 or 12 weeks are presented in Table 2. In subjects treated with MAVYRET, 45% reported an adverse reaction, of which 99% had adverse reactions of mild or moderate severity. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 0%, < 1% and 1% for the MAVYRET 8 week arm, MAVYRET 12 week arm and DCV + SOF arm, respectively.

Table 2. Adverse Reactions Reported in ≥5% of Treatment-Naïve Adults Without Cirrhosis Receiving MAVYRET for 8 Weeks or 12 Weeks in ENDURANCE-3

Adverse Reaction	MAVYRET* 8 Weeks (N = 157) %	MAVYRET 12 Weeks (N = 233) %	DCV ¹ + SOF ² 12 Weeks (N = 115) %
Headache	16	17	15
Fatigue	11	14	12
Nausea	9	12	12
Diarrhea	7	3	3

¹ DCV=daclatasvir

² SOF=sofosbuvir

* The 8 week arm was a non-randomized treatment arm.

Adverse Reactions in HCV-Infected Adults with Severe Renal Impairment Including Subjects on Dialysis

The safety of MAVYRET in subjects with chronic kidney disease (Stage 4 or Stage 5 including subjects on dialysis) with genotypes 1, 2, 3, 4, 5 or 6 chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) was assessed in 104 subjects (EXPEDITION-4) who received MAVYRET for 12 weeks. The most common adverse reactions observed in greater than or equal to 5% of subjects receiving 12 weeks of treatment with MAVYRET were pruritus (17%), fatigue (12%), nausea (9%), asthenia (7%), and headache (6%). In subjects treated with MAVYRET who reported an adverse reaction, 90% had adverse reactions of mild or moderate severity (Grade 1 or 2). The proportion of subjects who permanently discontinued treatment due to adverse reactions was 2%.

Laboratory Abnormalities

Serum bilirubin elevations

Elevations of total bilirubin at least 2 times the upper limit of normal occurred in 3.5% of subjects treated with MAVYRET versus 0% in placebo; these elevations were observed in 1.2% of subjects across the Phase 2 and 3 trials. MAVYRET inhibits OATP1B/3 and is a weak inhibitor of UGT1A1 and may have the potential to impact bilirubin transport and metabolism, including direct and indirect bilirubin. No subjects experienced jaundice and total bilirubin levels decreased after completing MAVYRET.

DRUG INTERACTIONS

Mechanisms for the Potential Effect of MAVYRET on Other Drugs

Glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. Coadministration with MAVYRET may increase plasma concentration of drugs that are substrates of P-gp, BCRP, OATP1B1 or OATP1B3. Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1.

Fluctuations in INR values may occur in patients receiving warfarin concomitant with HCV treatment, including treatment with MAVYRET. If MAVYRET is coadministered with warfarin, close monitoring of INR values is recommended during treatment and post-treatment follow-up.

Mechanisms for the Potential Effect of Other Drugs on MAVYRET

Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP. Glecaprevir is a substrate of OATP1B1/3. Coadministration of MAVYRET with drugs that inhibit hepatic P-gp, BCRP, or OATP1B1/3 may increase the plasma concentrations of glecaprevir and/or pibrentasvir.

Coadministration of MAVYRET with drugs that induce P-gp/CYP3A may decrease glecaprevir and pibrentasvir plasma concentrations.

Carbamazepine, efavirenz, and St. John's wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of MAVYRET. The use of these agents with MAVYRET is not recommended [see Warnings and Precautions].

Established and Other Potential Drug Interactions

Table 3 provides the effect of MAVYRET on concentrations of coadministered drugs and the effect of coadministered drugs on glecaprevir and pibrentasvir [see Contraindications].

Table 3. Potentially Significant Drug Interactions Identified in Drug Interaction Studies

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Antiarrhythmics:		
Digoxin	↑ digoxin	Measure serum digoxin concentrations before initiating MAVYRET. Reduce digoxin concentrations by decreasing the dose by approximately 50% or by modifying the dosing frequency and continue monitoring.
Anticoagulants:		
Dabigatran etexilate	↑ dabigatran	If MAVYRET and dabigatran etexilate are coadministered, refer to the dabigatran etexilate prescribing information for dabigatran etexilate dose modifications in combination with P-gp inhibitors in the setting of renal impairment.
Anticonvulsants:		
Carbamazepine	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Antimycobacterials:		
Rifampin	↓ glecaprevir ↓ pibrentasvir	Coadministration is contraindicated because of potential loss of therapeutic effect [see Contraindications].
Ethinyl Estradiol-Containing Products:		
Ethinyl estradiol-containing medications such as combined oral contraceptives	↔ glecaprevir ↔ pibrentasvir	Coadministration of MAVYRET may increase the risk of ALT elevations and is not recommended.
Herbal Products:		
St. John's wort (<i>hypericum perforatum</i>)	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
HIV-Antiviral Agents:		
Atazanavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is contraindicated due to increased risk of ALT elevations [see Contraindications].
Darunavir Lopinavir Ritonavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is not recommended.
Efavirenz	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
HMG-CoA Reductase Inhibitors:		
Atorvastatin Lovastatin Simvastatin	↑ atorvastatin ↑ lovastatin ↑ simvastatin	Coadministration may increase the concentration of atorvastatin, lovastatin, and simvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Coadministration with these statins is not recommended.
Pravastatin	↑ pravastatin	Coadministration may increase the concentration of pravastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Reduce pravastatin dose by 50% when coadministered with MAVYRET.
Rosuvastatin	↑ rosuvastatin	Coadministration may significantly increase the concentration of rosuvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with MAVYRET at a dose that does not exceed 10 mg.
Fluvastatin Pitavastatin	↑ fluvastatin ↑ pitavastatin	Coadministration may increase the concentrations of fluvastatin and pitavastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Use the lowest approved dose of fluvastatin or pitavastatin. If higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment.
Immunosuppressants:		
Cyclosporine	↑ glecaprevir ↑ pibrentasvir	MAVYRET is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day.
↑ = increase; ↓ = decrease; ↔ = no effect		

Drugs with No Observed Clinically Significant Interactions with MAVYRET

No dose adjustment is required when MAVYRET is coadministered with the following medications: abacavir, amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, elvitegravir/cobicistat, emtricitabine, feldopidine, lamivudine, lamotrigine, losartan, methadone, midazolam, naloxone, norethindrone or other progestin-only contraceptives, omeprazole, raltegravir, rilpivirine, sofosbuvir, tacrolimus, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide, and valsartan.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

No adequate human data are available to establish whether or not MAVYRET poses a risk to pregnancy outcomes. In animal reproduction studies, no adverse developmental effects were observed when the components of MAVYRET were administered separately during organogenesis at exposures up to 53 times (rats; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) the human exposures at the recommended dose of MAVYRET [see Data]. No definitive conclusions regarding potential developmental effects of glecaprevir could be made in rabbits, since the highest achieved glecaprevir exposure in this species was only 7% (0.07 times) of the human exposure at the recommended dose. There were no effects with either compound in rodent pre/post-natal developmental studies in which maternal systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 47 and 74 times, respectively, the exposure in humans at the recommended dose [see Data].

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated

<p>background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.</p> <p>Data</p> <p>Glecaprevir</p> <p>Glecaprevir was administered orally to pregnant rats (up to 120 mg/kg/day) and rabbits (up to 60 mg/kg/day) during the period of organogenesis (gestation days (GD) 6 to 18, and GD 7 to 19, respectively). No adverse embryo-fetal effects were observed in rats at dose levels up to 120 mg/kg/day (53 times the exposures in humans at the recommended human dose (RHD)). In rabbits, the highest glecaprevir exposure achieved was 7% (0.07 times) of the exposure in humans at RHD. As such, data in rabbits during organogenesis are not available for glecaprevir systemic exposures at or above the exposures in humans at the RHD.</p> <p>In the pre/post-natal developmental study in rats, glecaprevir was administered orally (up to 120 mg/kg/day) from GD 6 to lactation day 20. No effects were observed at maternal exposures 47 times the exposures in humans at the RHD.</p> <p>Pibrentasvir</p> <p>Pibrentasvir was administered orally to pregnant mice and rabbits (up to 100 mg/kg/day) during the period of organogenesis (GD 6 to 15, and GD 7 to 19, respectively). No adverse embryo-fetal effects were observed at any studied dose level in either species. The systemic exposures at the highest doses were 51 times (mice) and 1.5 times (rabbits) the exposures in humans at the RHD.</p> <p>In the pre/post-natal developmental study in mice, pibrentasvir was administered orally (up to 100 mg/kg/day) from GD 6 to lactation day 20. No effects were observed at maternal exposures approximately 74 times the exposures in humans at the RHD.</p> <p>Lactation</p> <p>Risk Summary</p> <p>It is not known whether the components of MAVYRET are excreted in human breast milk, affect human milk production, or have effects on the breastfed infant. When administered to lactating rodents, the components of MAVYRET were present in milk, without effect on growth and development observed in the nursing pups <i>[see Data]</i>.</p> <p>The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MAVYRET and any potential adverse effects on the breastfed child from MAVYRET or from the underlying maternal condition.</p> <p>Data</p> <p>No significant effects of glecaprevir or pibrentasvir on growth and post-natal development were observed in nursing pups at the highest doses tested (120 mg/kg/day for glecaprevir and 100 mg/kg/day for pibrentasvir). Maternal systemic exposure (AUC) to glecaprevir and pibrentasvir was approximately 47 or 74 times the exposure in humans at the RHD. Systemic exposure in nursing pups on post-natal day 14 was approximately 0.6 to 2.2 % of the maternal exposure for glecaprevir and approximately one quarter to one third of the maternal exposure for pibrentasvir.</p>	<p>Glecaprevir or pibrentasvir was administered (single dose; 5 mg/kg oral) to lactating rats, 8 to 12 days post parturition. Glecaprevir in milk was 13 times lower than in plasma and pibrentasvir in milk was 1.5 times higher than in plasma. Parent drug (glecaprevir or pibrentasvir) represented the majority (>96%) of the total drug-related material in milk.</p> <p>Pediatric Use</p> <p>Safety and effectiveness of MAVYRET in children less than 18 years of age have not been established.</p> <p>Geriatric Use</p> <p>In clinical trials of MAVYRET, 328 subjects were age 65 years and over (14% of the total number of subjects in the Phase 2 and 3 clinical trials) and 47 subjects were age 75 and over (2%). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects. No dosage adjustment of MAVYRET is warranted in geriatric patients.</p> <p>Renal Impairment</p> <p>No dosage adjustment of MAVYRET is required in patients with mild, moderate or severe renal impairment, including those on dialysis.</p> <p>Hepatic Impairment</p> <p>No dosage adjustment of MAVYRET is required in patients with mild hepatic impairment (Child-Pugh A). MAVYRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B). Safety and efficacy have not been established in HCV-infected patients with moderate hepatic impairment. MAVYRET is contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to higher exposures of glecaprevir and pibrentasvir <i>[see Contraindications]</i>.</p> <p>OVERDOSAGE</p> <p>In case of overdose, the patient should be monitored for any signs and symptoms of toxicities. Appropriate symptomatic treatment should be instituted immediately. Glecaprevir and pibrentasvir are not significantly removed by hemodialysis.</p> <p>PATIENT COUNSELING INFORMATION</p> <p>Advise the patient to read the FDA-approved patient labeling (Patient Information).</p> <p>Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV</p> <p>Inform patients that HBV reactivation can occur in patients coinfectd with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of hepatitis B virus infection <i>[see Warnings and Precautions]</i>.</p> <p>Drug Interactions</p> <p>Inform patients that MAVYRET may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication or herbal products <i>[see Contraindications, Warnings and Precautions and Drug Interactions]</i>.</p>	<p>Administration</p> <p>Advise patients to take MAVYRET recommended dosage (three tablets) once daily with food as directed. Inform patients that it is important not to miss or skip doses and to take MAVYRET for the duration that is recommended by the physician.</p> <p>If a dose is missed and it is:</p> <ul style="list-style-type: none">• Less than 18 hours from the usual time that MAVYRET should have been taken – advise the patient to take the dose as soon as possible and then to take the next dose at the usual time.• More than 18 hours from the usual time that MAVYRET should have been taken – advise the patient not to take the missed dose and to take the next dose at the usual time. <p>Manufactured by AbbVie Inc., North Chicago, IL 60064 MAVYRET is a trademark of AbbVie Inc.</p> <p>© 2017 AbbVie Inc. All rights reserved. Ref: 03-B632 Revised: December, 2017</p> <p>46A-1937720 MASTER</p>
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MAVYRET[™]
glecaprevir/pibrentasvir
100 mg/40 mg tablets

**DON'T
LOOK
BACK**

FOR CHRONIC HCV

**TREAT ALL GENOTYPES
IN AS FEW AS 8 WEEKS**

**THE ONLY 8-WEEK PANGENOTYPIC (GT1-6) REGIMEN
FOR TREATMENT-NAÏVE, NON-CIRRHOTIC PATIENTS**

Duration is dependent on treatment history, genotype, or the presence of compensated cirrhosis. Refer to the full Prescribing Information for further dosing information.

INDICATION¹

MAVYRET[™] (glecaprevir and pibrentasvir) tablets are indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both.

IMPORTANT SAFETY INFORMATION¹

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV: Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with MAVYRET. HBV reactivation has been reported in HCV/HBV coinfecting patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfecting patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

CONTRAINDICATIONS¹

MAVYRET is contraindicated:

- In patients with severe hepatic impairment (Child-Pugh C)
- With the following drugs: atazanavir or rifampin

WARNINGS AND PRECAUTIONS¹

Risk of Reduced Therapeutic Effect Due to Concomitant Use of MAVYRET with Carbamazepine, Efavirenz-containing Regimens, or St. John's Wort

- Carbamazepine, efavirenz, and St. John's Wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of MAVYRET. The use of these agents with MAVYRET is not recommended.

ADVERSE REACTIONS¹

Most common adverse reactions observed with MAVYRET:

- >10% of subjects: headache and fatigue
- ≥5% of subjects: headache, fatigue, and nausea

Please see following pages for a brief summary of the full Prescribing Information.

GT=genotype.

Reference: 1. MAVYRET [package insert]. North Chicago, IL: AbbVie Inc.; 2017.