High-Cost Therapies: Innovative Payment Strategies

Cystic Fibrosis: Moving Toward More Personalized Care

Asthma: Increasing Competition on the Medical Benefit

Human Immunodeficiency Virus: The Evolving Treatment Landscape

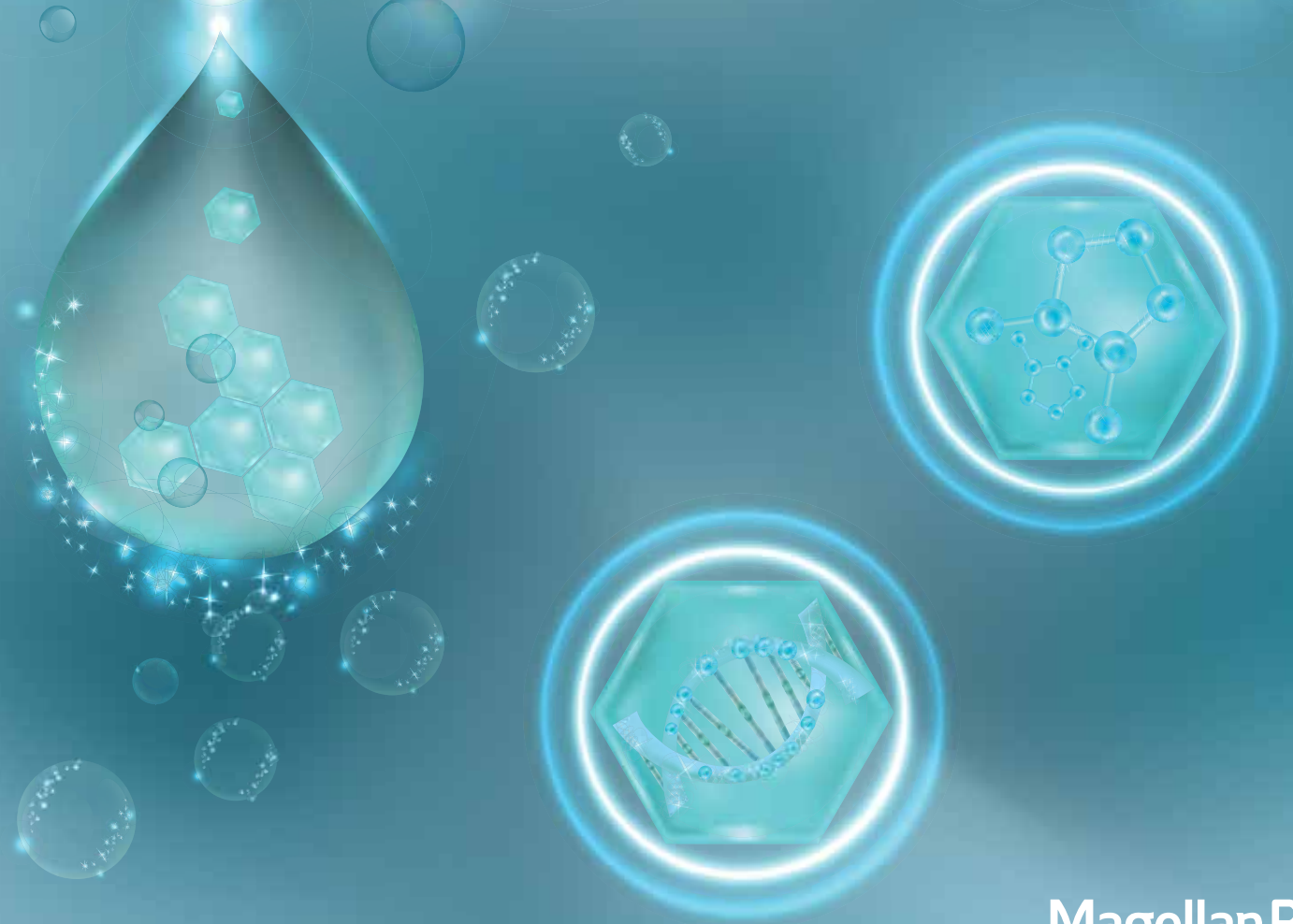
Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Summer 2018

Biosimilars:

Impact, Lessons Learned, and Opportunities



Magellan Rx MANAGEMENT℠
magellanrx.com

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.
- 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.

*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.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

REGENERON

08/2016
US-PMA-12565

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.

1 INDICATIONS AND USAGE

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.

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 ½-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 periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept 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 edothelial 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. Aflibercept 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, sternebrae, 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. Aflibercept 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 aflibercept 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

Manufactured by:
Regeneron Pharmaceuticals, Inc.
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Tarrytown, NY 10591-6707

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Welcome to the **Magellan Rx** Report

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Features

Mostafa Kamal
Chief Executive Officer
Magellan Rx Management

Dear Managed Care Colleagues,

Welcome to our summer issue of the Magellan Rx™ Report! Once again, the Food and Drug Administration (FDA) got off to a fast start in 2018, with 20 novel drug approvals in the first half of the year, and more than 40 pending novel product reviews remaining for the second half of the year. Fortunately, Magellan Rx Management was poised to prepare payors for these approvals with the quarterly MRx Pipeline, which offers clinical insights and competitive intelligence on anticipated specialty and traditional drugs in the pipeline. Magellan Rx Management was also prepared to share a one-of-a-kind pharmacy report to help employers better plan for the future in the first Employer Market Insights Report. Key highlights from the report can be found in the Newsstand section of the magazine.

In this issue of the Magellan Rx™ Report, the cover story reviews the slower-than-expected uptake of biosimilars in the U.S. and the cost saving opportunities that may exist as a result of the increased competition in the biosimilar space. The article also includes information about currently available FDA-approved biosimilars and a list of biosimilars that are in late-stage development.

A second article of focus explores innovative payment strategies for high-cost therapies and the various challenges and opportunities associated with these strategies.

Another article of interest discusses the increased competition on the medical benefit with the various injectable therapies available for the treatment of asthma. The article also highlights various biologics that are currently being investigated for the treatment of asthma.

Other notable topics featured in this issue include a spotlight on the regulatory updates in the field of managed care; an update on the existing therapies and the treatment pipeline for cystic fibrosis; and an update on currently available therapies and pipeline agents for the treatment of human immunodeficiency virus (HIV).

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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Get more insight on the industry's most innovative and groundbreaking managed care solutions for some of the most complex areas of healthcare. Email us at **MagellanRxReport@magellanhealth.com** to receive the latest issue, delivered right to your inbox.

Managed Care Newsstand

Magellan Health Named to the Fortune 500 List of America's Largest Companies

In May 2018, Magellan Health, Inc. announced that it has been named to the annual Fortune 500 list of America's largest corporations by revenue for the first time in the company's history. This year marks the 64th running of the list, which began in 1955.

"It is such an honor for all of us at Magellan to be among this list of impressive and innovative companies that represent the very best in America," said Barry M. Smith, chairman and chief executive officer of Magellan Health. "At Magellan, we will continue to innovate and introduce products that resonate, disrupt the industry and continue to make a difference in people's lives."

Magellan is a leader in managing complex population health, concentrating on all areas across healthcare and pharmaceutical management. With over 10,000 employees and a 2017 revenue of $5.8 billion, Magellan's consumer-centric model of care achieves improved outcomes by integrating healthcare across physical, behavioral and pharmaceutical services. Magellan manages the highest trend components of healthcare expenditures using agile, clinically-based technology and applying advanced analytics in its development of next-generation solutions.

In addition, Magellan has differentiated itself in the specialty drug management space. Today, roughly half the total pharmacy spend is driven by specialty drugs, with half of that specialty spend covered under medical benefits, which is typically unmanaged by pharmacy benefit managers or health plans. The company has pioneered innovative strategies to tackle the high-trend areas of specialty and medical pharmaceuticals and continues to offer high-touch clinical programs focused on improved outcomes and value.

"This recognition speaks to the dedication of our associates who serve our members and customers each day with a focus on leading humanity to healthy, vibrant lives," said Smith. "We are unique in our model of care that's both high-touch and high-tech, supported by an innovative and inclusive culture."

According to Fortune, in 2018 companies on the 500 list represent two-thirds of the U.S. GDP with $12.8 trillion in revenues, $1.0 trillion in profits and $21.6 trillion in market value, and employing 28.2 million people worldwide.

"It is such an honor for all of us at Magellan to be among this list of impressive and innovative companies that represent the very best in America."

- Barry M. Smith

Magellan Rx Management Releases New Employer Market Insights Report

In April 2018, Magellan Rx Management released its first Employer Market Insights Report, which highlights key areas of pharmacy trend and spend, and provides exclusive forecasting information to help employers better plan for the future.

The report highlights current and projected trend insights for both traditional and specialty drugs, and explores the factors driving employer costs. Analysis of key therapeutic conditions provides an additional layer of forecasting, including a preview of the impact of new pipeline drugs.

"Today's dynamic and complex healthcare environment has led to new developments in drug therapies that are both exciting and challenging. This is especially true for employers who are increasingly concerned about rising prescription costs," said Mostafa Kamal, chief executive officer of Magellan Rx Management. "Our Employer Market Insights Report provides a unique perspective of pharmacy management, allowing employers to better plan for the future."

Key highlights from the Employer Market Insights Report:

1. Specialty drug costs on the pharmacy benefit are projected to reach close to 50% of total drug costs by 2020
2. The overall growth of pharmacy benefit costs is expected to slow in 2019 and 2020
3. By 2020, the specialty cost per claim will reach $6,300, almost four times the cost in 2008
4. Autoimmune: anti-inflammatory and diabetes will drive overall drug costs, comprising between 30 and 35% of total pharmacy benefit costs
5. New specialty pipeline drugs will contribute 25% of forecasted overall pharmacy benefit growth by 2020

Important insights for employers from the report include:

1. Comprehensive forecasting for key areas of pharmacy trend and spend
2. Effective cost-management strategies to tackle these trends
3. Pilots and partnerships that demonstrate an innovative approach to pharmacy management

In addition to cost trends, the report features a unique focus on specialty drugs, specifically the drug activity taking place on the medical benefit, one of the fastest and largest growing healthcare cost drivers. Medical pharmacy insights were collected through a primary survey with employer groups, showing current and future cost-control management strategies for medical specialty drugs.

"By leveraging our advanced analytics framework, we uncover the hidden stories within the complex arena of prescription costs," said Lori Bymark, senior vice president of advanced analytics at Magellan Rx Management. "These stories transform information into meaningful intelligence that empowers our customers to make better decisions, underscoring our commitment to provide value-driven solutions."

Managed Care Newsstand

Magellan Rx Management Announces Results from Hemophilia Management Program

On "World Hemophilia Day (April 17)," Magellan Rx Management announced the results from the first six months of its hemophilia management program, launched in collaboration with Health New England, a nonprofit health plan serving the commercial, Medicaid, and Medicare markets.

Hemophilia is a rare genetic bleeding disorder, for which treatment is expensive and difficult to manage. The average annual cost per member with severe hemophilia can exceed $250,000, and may be upwards of $1 million for members who have developed inhibitors. Personalized care programs for patients with hemophilia aim to reduce unnecessary costs while improving the overall quality of care.

"We're excited to bring hemophilia care into the spotlight and highlight the early results achieved with Health New England through our hemophilia management program," said Haita Makanji, vice president of clinical specialty solutions at Magellan Rx Management. "Through personalized interventions, we're able to better determine the individual member needs and coordinate across key stakeholders to deliver a truly personalized care program that ensures members with hemophilia receive best-in-class care and achieve optimal outcomes."

Since launching the hemophilia management program in August 2017, Magellan Rx Management and Health New England have standardized care across various stakeholders without compromising patient outcomes, resulting in:

1. Optimized doses through assay management or pharmacokinetic testing in 50% of members
2. Reduced average assay dispensed in prophylaxis patients from 5% to 1%, reducing the potential for waste
3. No breakthrough bleeding reported from members who had a dose reduction

"In the past eight months of collaboration with Magellan [Rx], we've achieved our goals of ensuring high quality of care for members with hemophilia while minimizing potential waste created through excess dispensing and inappropriate dosing," said Andrew J. Colby, RPh, MBA, Health New England's pharmacy director. "By announcing our hemophilia management program results on World Hemophilia Day, we hope to raise the profile of this condition and look to continue to make strides in standardizing best treatment practices to benefit members across the country."

"Through personalized interventions, we're able to better determine the individual member needs and coordinate across key stakeholders to deliver a truly personalized care program that ensures members with hemophilia receive best-in-class care and achieve optimal outcomes."

The hemophilia management program aims to enhance overall quality and personalization of hemophilia care by coordinating with prescribers, members, and pharmacies, while also reducing unnecessary costs. Key elements include:

1. Helping payors analyze information related to member bleed history and hemophilia treatment patterns
2. Standardizing dispensing and optimal dose protocols to promote best practices and improve transparency in hemophilia care
3. Updating policies to encourage individualized treatment regimens based on member-specific metabolic factors

Additional results from this program will be shared in a future issue of the Magellan Rx™ Report.

The average annual cost per member with severe hemophilia can exceed $250,000, and may be upwards of $1 million for members who have developed inhibitors.

CMS Announces Revised Drug Dashboards, as FDA Unveils New Website Listing More Than 40 Drug Companies Accused of Blocking Generics

Announced May 15 and May 17, respectively.

CMS announced it has redesigned its Drug Spending Dashboards in an effort to improve transparency on prescription drug prices. The revised dashboards provide year-over-year information on drug pricing, including the percentage change in spending on drugs per dosage unit, in both Medicare and Medicaid. The dashboards include an expanded list of drugs and also identify which manufacturers have increased their prices, suggesting dozens of Medicare and Medicaid drugs more than doubled in price between 2015 and 2016. CMS Administrator Seema Verma described the changes as "an important step to bringing transparency and accountability to what has been a largely hidden process."

Later in the week, the FDA launched a website listing more than 40 brand-name drug makers that, potentially, have been blocking access to their drug samples in an effort to prevent generic competition. The May 17 announcement also stated that the FDA is notifying the U.S. Federal Trade Commission (FTC) about many of the cases, and that it has encouraged generic drug makers to raise concerns with the FTC. FDA Commissioner Scott Gottlieb stated: "Branded companies are on notice that there will be a website at FDA that's going to identify when multiple generic entrants are having trouble getting access to their physical samples."

Draft FDA Guidances Seek to Promote Generic Competition

On May 31, the FDA announced two new draft guidance documents outlining policies intended to prevent brand-name drug manufacturers from using risk evaluation and mitigation strategies (REMS) to block competition from generic drug makers. Of these, one new draft guidance document discusses the possible benefits of a shared system REMS for prescription drug products, and provides general principles and recommendations to assist the industry with the development of these programs. FDA Commissioner Scott Gottlieb, MD notes that the goal of this guidance is to "improve the clarity and efficiency for developing shared system REMS, which will enable timelier market entry for products that are part of these REMS."

Another new draft guidance document discusses the factors the FDA will consider in evaluating a request for a waiver of the existing requirement that the applicant for an abbreviated new drug application and its reference listed drug use a single, shared system for a REMS. This guidance also provides recommendations to generic drug applicants regarding the submission and content of waiver requests.

CMS announced it has redesigned its Drug Spending Dashboards in an effort to improve transparency on prescription drug prices.

Biosimilars

Impact, Lessons Learned, and Opportunities

According to the U.S. Food and Drug Administration (FDA), biological products are the fastest-growing class of therapeutics.[1] Although the development of biological products did not really begin to launch until the early 2000s, by 2016, biologics made up 25% of the total pharmaceutical pipeline. Biologics may offer important advantages compared to traditional small molecule drugs. The majority of traditional small molecules work as inhibitors because they are small enough to insert themselves into and interfere with molecular processes.

Kristen M. Reimers, RPh
Vice President, Medical Pharmacy Strategy
Magellan Rx Management

Because small molecules are, as their name implies, relatively small in size and there is a large number of molecular components inside any given cell, it can be very challenging to create a small molecule that is able to target a specific molecular component with a significant degree of precision. As such, off-target interactions may occur, resulting in a variety of side effects.[1] Because biological products are larger than small molecules, often 200 to 1,000 times larger, there are several specific points of contact with the intended target, allowing for greater precision.[2] In addition, biological products can be designed to promote inhibitory effects or to stimulate an immune response. These key differences allow for the development of biological products that are able to target molecular processes that conventional small molecules cannot effectively target. Furthermore, the list of therapeutic targets for biological products is seemingly endless, with oncology indications dominating the list.[2,3]

With great innovation comes great cost, a trend that has become all too familiar. Biological products are generally much more expensive than traditional small molecule drugs, costing approximately 22 times more on average and generating significant profit margins of as much as 40%.[4] Biological products currently account for approximately 40% of prescription drug spending in the U.S. and 70% of prescription drug spending growth from 2010 to 2015. Given the high costs associated with biological products, there is a great deal of interest in the development of lower-cost "generics," known as biosimilars.[4,5]

With the influx of biological products that occurred in the early 2000s, many of these agents have patents that have since expired.[5] While there has been a well-established abbreviated pathway for small molecule generics to reach the market since the enactment of the Hatch-Waxman Act in 1984, a pathway for biosimilars was not established until the Patient Protection and Affordable Care Act (ACA) of 2010. The ACA amended the Public Health Service Act, establishing an abbreviated approval pathway for biological products with clinical evidence demonstrating that they are either highly similar (i.e., biosimilar) or interchangeable with an approved biological product. The new provisions established with this amendment are referred to as the Biologics Price Competition and Innovation Act (BPCIA) of 2009.[6]

In order to receive FDA approval, the manufacturer must demonstrate that the biosimilar product is highly

TABLE 1. FDA-APPROVED BIOSIMILARS[7-9]			
Drug Name (Manufacturer)	Reference Product	Approval Date	Current Market Status
Zarxio® (filgrastim-sndz) (Sandoz)	Neupogen®	3/2015	Launched 9/2015
Inflectra® (infliximab-dyyb) (Celltrion, Hospira)	Remicade®	4/2016	Launched 11/2016
Erelzi® (etanercept-szzs) (Sandoz)	Enbrel®	8/2016	Not yet launched; ongoing patent litigation
Amjevita® (adalimumab-atto) (Amgen)	Humira®	9/2016	Anticipated launch on 1/31/2023 pursuant to global settlement agreement
Renflexis® (infliximab-abda) (Samsung Bioepis)	Remicade®	5/2017	Launched 7/2017
Cyltezo® (adalimumab-adbm) (Boehringer Ingelheim)	Humira®	8/2017	Not yet launched; ongoing patent litigation
Mvasi® (bevacizumab-awwb) (Amgen, Allergan)	Avastin®	9/2017	Not yet launched; ongoing patent litigation
Ogivri® (trastuzumab-dkst) (Mylan, Biocon)	Herceptin®	12/2017	Anticipated launch date undisclosed under settlement agreement
Ixifi® (infliximab-qbtx) (Pfizer)	Remicade®	12/2017	Not expected to launch in the U.S.
Retacrit® (epoetin alfa-epbx) (Pfizer)	Procrit®	5/2018	Manufacturer anticipates launch in 2018
Fulphila™ (pegfilgrastim-jmdb) (Mylan, Biocon)	Neulasta®	6/2018	Manufacturer anticipates launch in summer 2018

similar to, with no clinically meaningful differences from, the existing FDA-approved reference biological product.[1] To demonstrate high similarity, the structure and function of both the reference product and proposed biosimilar are analyzed extensively, with qualities such as purity, chemical identity, and biological activity being characterized. Per the FDA, minor differences between the biosimilar and the reference product are permitted for clinically inactive components, such as a stabilizer or buffer, recognizing that the manufacturing process may differ between manufacturers. Biosimilars also require human studies that evaluate both pharmacokinetics and pharmacodynamics, as well as the potential for immunogenicity, in order to demonstrate that there are no clinically meaningful differences in safety and/or effectiveness.[1]

The BPCIA also established a pathway by which a biosimilar could be classified as interchangeable, allowing for the substitution of the biosimilar for the reference product at the pharmacy without requiring the prescriber's approval of the substitution.[1,6] Interchangeable biosimilars must meet additional requirements to demonstrate that the interchangeable product is expected to produce the same clinical result as the reference product in any patient. For biological reference products expected to be administered to a patient more than once, switching studies are also required to evaluate the safety and risk of reduced efficacy that could occur if a patient were to switch back and forth between the reference product and the interchangeable product.[1]

While the establishment of an abbreviated regulatory pathway occurred in 2010, it took two more years for the FDA to issue industry guidance on the development and registration process for biosimilar products.[7] Following the issuance of the FDA draft guidance in 2012, the first biosimilar Zarxio® (filgrastim-sndz) was approved in 2015. As of April 2018, eleven biosimilars have received FDA approval; however, only three of them have been launched on the U.S. market thus far (see Table 1).[7-9]

Biosimilars have been very slow to reach the U.S. market since the enactment of the BPCIA, largely due to the

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many challenges associated with the development of biosimilars.[10] In addition to the differences between biological products and traditional small molecule drugs that were noted above, biological products also differ significantly in the way they are developed. Specifically, the development of biological products is far more complex; small molecule drugs are generally manufactured through chemical synthesis and have a well-defined chemical structure, allowing for the quality and consistency of the product to be validated in the laboratory. In contrast, biological products are very large, complex structures that are manufactured in a living system such as human and animal cells, yeast, and bacteria. In addition, many FDA-approved biological products are created using recombinant deoxyribonucleic acid technology.[10,11] Given the complex manufacturing process associated with the creation of a biological product, it is often very difficult or even impossible to characterize and validate the finished product in a laboratory. Because there is no specific "recipe" for a biological product, no two vials are precisely the same.[10] As such, the best way to ensure consistency, quality, and purity of a biological product is to tightly control the manufacturing process to ensure that there is no variation. Given the emphasis on the manufacturing process, the process itself is often confidential and part of the biological product's patent. Without significant knowledge of and experience with the manufacturing process, it is very challenging for a biosimilar manufacturer to replicate the reference product.[10,11]

In addition to the more complex manufacturing process associated with biosimilars and their reference products, there are much more complex clinical trial requirements for approval of a biosimilar compared to a small molecule generic.[12] While the cost to develop a small molecule generic drug varies between $1 million and $4 million, it is estimated that it may cost closer to $100 million to $250 million to develop a biosimilar product. As such, while generic small molecule drugs may come to market with a 50% to 90% discount compared to the originator products, the biosimilars that have reached the U.S. market thus far have had much smaller discounts compared to their reference products, ranging from 15% to 30%.[12]

Uptake of biosimilars in the U.S. has been much slower than what has been observed in the European Union (EU). As of late 2017, a total of 32 biosimilars had been approved in the EU based on 12 reference biological products.[10] There are several factors playing a role in the relatively slow uptake of biosimilars in the U.S. compared to the EU, beginning with the way biosimilars are classified. While the FDA classifies biosimilars based on whether they are interchangeable, European regulators do not offer such a distinction. Instead, European legislation allows individual member states to determine whether biosimilars and originators may be used interchangeably; however, biosimilars in the EU are assumed to be substitutable for the originator biological product. In the U.S., there are currently no biosimilars that are classified as interchangeable.[9] If a biosimilar is not classified as interchangeable, the prescriber must write the prescription for the specific biosimilar product in order for it to be filled at the pharmacy. Given that the originator products have been on the market for much longer than their biosimilar counterparts have, the degree of variation that is considered acceptable among products, and the seriousness of the disease states that these products are used to treat, prescribers may be more comfortable continuing to prescribe the originator products. Furthermore, prescribers are likely to have more brand recognition of the originator product and may more readily prescribe the originator product rather than looking up brand names of new biosimilars that they may not be familiar with.[10]

From the patient's perspective, when biosimilars are dispensed instead of the originator product, the FDA requires that patients be notified of the specific product they are receiving.[10] While many patients may be familiar and comfortable with the process of receiving a generic small molecule product substituted for the brand name product, receiving a biosimilar with a different brand name from the originator product may cause some confusion and concern. In situations where patients have been receiving the originator product for several years, they may be even less comfortable with making a change to a biosimilar. As with prescribers, this level of discomfort will likely increase with the severity of the disease being treated.[10]

From a payor perspective, health plans recognize that with more competition the costs of biosimilars may decrease. The fact that biosimilars will now have their own assigned code instead of shared codes will also help with competition. Manufacturers of well-established originator products may offer significant rebates to payors that may encourage them to prefer the originator product over the biosimilar, especially if the rebate for the originator product exceeds the 15 to 30% discount that is typically seen with biosimilars.[12] As a result, it has been very difficult for biosimilars to gain any significant market share following FDA approval. Health plans may want to move to biosimilar strategies to achieve a lower net cost overall; although it may be easier to implement this strategy with oncology drugs with shorter durations of treatment.

Another concern for health plans is

provider buy-in. Patients defer to their physicians regarding appropriate treatment, and the success of biosimilars depends on physicians' confidence in prescribing these therapies. A recent survey of specialists and primary care physicians revealed that 78% of providers were familiar with the term "biosimilar," while only 17% of prescribing specialists felt "very likely" to prescribe them.[13] Furthermore, only 12% of prescribing specialists reported feeling "very confident" that biosimilars are as safe as the originators, and 80% reported that they would need to learn more about biosimilars.[13] The results of this survey highlight the need for more education regarding the safety, efficacy, and availability of biosimilars, as well as the drivers and barriers of biosimilar use among physicians across different specialties, and how physicians' perceptions of biosimilars translate to expected use in the real-world setting.

There is also a need for advocacy group buy-in. Following recent FDA approvals of biosimilars, patient advocacy groups have called on Congress to address patient safety concerns.[14] The national coalition group, Patients for Biologics Safety & Access, has proposed various actions to the FDA, including one major proposal: that there be no automatic substitution of biosimilars for biologics, as the choice of products should be made by a physician in consultation with his or her patient, and should not be determined by a pharmacist, regulator, or insurer.[14] While most will agree that the decision should be made by the provider and the patient, this proposal, if implemented by the FDA, would have a tremendous impact on what biosimilar switching or "new starts only" programs can be implemented by health plans. It is crucial that additional discussions take place with patient advocacy groups to ensure that all key stakeholders understand the safety and efficacy of biosimilars, as well as the potential cost-saving opportunities they provide to the healthcare system as a whole.

Another significant hurdle for biosimilars coming to market is the extensive exchange of information that occurs under the BPCIA of 2009, commonly referred to as the "patent dance." The intent behind this information exchange between the biosimilar applicant and the originator product sponsor is to proactively resolve any potential patent disputes in an expeditious manner.[15,16] As part of this process, the biosimilar applicant provides a copy of the supplemental biologics license application (sBLA) to the originator product sponsor within 20 days of the FDA's acceptance of the sBLA. Along with the sBLA, additional information describing the process or processes used to manufacture the biosimilar are also submitted to the originator product sponsor for review. For the following six months or so, the two parties exchange their respective patent lists and contentions, theoretically resulting in a final, agreed-upon list of patents that the originator product sponsor will bring an action for patent infringement within 30 days of finalizing the list. A second round of litigation may be brought, including preliminary injunction on patents not included in the final list but included in the earlier exchanges, when the biosimilar applicant gives notice of commercial marketing.[15,16] It is important to note that following two different U.S. Supreme Court decisions in June and August 2017, it was determined that the biosimilar applicant cannot be forced to engage in the patent dance, nor can the applicant be forced to fully engage in the patent dance following initiation. There are several potential benefits and risks associated with the patent dance for the biosimilar applicant. For example, engaging in and complying with the disclosure requirements may give the biosimilar sponsor greater control of the patent litigation process, as well as extensive knowledge of what the originator product sponsor intends to pursue legally. Participation would also force the originator product sponsor to bring suit at the end of the patent dance, giving the biosimilar applicant greater control over timing of litigation. By resolving litigation proactively, biosimilars may be able to avoid being tangled in litigation post-FDA approval and launch as soon as they are approved. Conversely, opting not to participate would allow the biosimilar applicant to keep sensitive manufacturing information confidential.[15,16]

There continues to be significant focus on developing biosimilar agents within the pharmaceutical pipeline, with a handful of biosimilars expected to receive FDA approval later in 2018 (see Table 2).[17] Despite the slow uptake of biosimilars in the U.S. market, greater market competition may allow for better market penetration of these agents. Prescribers and payors can support increased market competition by educating themselves about biosimilar options and promoting use of these products among their patients or plan membership. As biosimilars gain more market share, we may see the discounts associated with them increase, resulting in the cost savings that patients and payors alike have been waiting for. Greater availability of biosimilars may improve patient access to these important therapies that may improve survival and quality of life in diseases that are often difficult to treat.

As biosimilars gain greater market share, we may see the discounts associated with biosimilars increase, resulting in the cost savings that patients and payors alike have been waiting for.

TABLE 2. BIOSIMILARS IN LATE-STAGE DEVELOPMENT[17]

Drug Name (Manufacturer)	Reference Product	Anticipated Approval	Originator Product Indications
Adalimumab (GP2017) (Novartis, Sandoz)	Humira®	November 16, 2018	RA, JIA, AS, PsO, CD (adults and children), UC, HS, noninfectious uveitis
Filgrastim (Adello)	Neupogen®	Q3 2018	Nonmyeloid malignancies in patients receiving myelosuppressive anticancer drugs; following induction/consolidation chemotherapy for AML; nonmyeloid malignancies in patients undergoing myeloablative chemotherapy followed by bone marrow transplant; to mobilize autologous hematopoietic progenitor cells for leukapheresis; in symptomatic patients with congenital, cyclic, or idiopathic neutropenia; patients acutely exposed to myelosuppressive doses of radiation (HSARS)
Filgrastim (Nivestim®) (Pfizer)	Neupogen®	September 2018	
Filgrastim (Grastofil®) (Apotex)	Neupogen®	Pending	
Insulin glargine (Basalog®)* (Mylan, Biocon)	Lantus®	Received CRL; no update regarding time line for resubmission	T1DM, T2DM
Insulin glargine (Lusduna Nexvue®)* (Merck)	Lantus®	Pending	T1DM, T2DM
Pegfilgrastim (Lapelga®) (Apotex)	Neulasta®	Pending	Nonmyeloid malignancies in patients receiving myelosuppressive anticancer drugs; HSARS
Trastuzumab (ABP 980) (Amgen, Allergan)	Herceptin®	Received CRL; no update regarding time line for resubmission	HER2-positive breast cancer; HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma
Trastuzumab (CT-P6) (Celltrion)	Herceptin®	BLA resubmitted in June 2018 after receiving CRL	
Trastuzumab (SB3) (Merck, Samsung Bioepis)	Herceptin®	October 20, 2018	
Adalimumab (Coherus)	Humira®	TBD; BLA submitted	RA, AS, PsO, PsA, JIA, CD, UC
Adalimumab (Fresenius Kabi)	Humira®	TBD; BLA submitted	RA, AS, PsO, PsA, JIA, CD, UC
Adalimumab (Fujifilm Kyowa Kirin Biologics)	Humira®	TBD; BLA submitted	RA, AS, PsO, PsA, JIA, CD, UC
Adalimumab (Momenta)	Humira®	TBD; BLA submitted	RA, AS, PsO, PsA, JIA, CD, UC
Adalimumab (Mylan, Biocon)	Humira®	TBD; BLA submitted	RA, AS, PsO, PsA, JIA, CD, UC
Adalimumab (Pfizer)	Humira®	TBD; BLA submitted	RA, AS, PsO, PsA, JIA, CD, UC
Adalimumab (Samsung Bioepis, Merck)	Humira®	TBD; BLA submitted	RA, AS, PsO, PsA, JIA, CD, UC
Bevacizumab (Boehringer Ingelheim)	Avastin®	TBD; BLA submitted	CRC; NSCLC; ovarian, fallopian tube, peritoneal cancer, glioblastoma, RCC
Bevacizumab (Fujifilm Kyowa Kirin Biologics)	Avastin®	TBD; BLA submitted	CRC; NSCLC; ovarian, fallopian tube, peritoneal cancer, glioblastoma, RCC
Bevacizumab (Mylan, Biocon)	Avastin®	TBD; BLA submitted	CRC; NSCLC; ovarian, fallopian tube, peritoneal cancer, glioblastoma, RCC
Bevacizumab (Pfizer)	Avastin®	TBD; BLA submitted	CRC; NSCLC; ovarian, fallopian tube, peritoneal cancer, glioblastoma, RCC

Epoetin alfa (Sandoz)	Procrit®	TBD; BLA submitted	Anemia due to CKD (dialysis-dependent)
Etanercept (Coherus)	Enbrel®	TBD; BLA submitted	RA, JIA, AS, PsO, PsA
Etanercept (Merck, Samsung Bioepis)	Enbrel®	TBD; BLA submitted	RA, JIA, AS, PsO, PsA
Infliximab (Amgen)	Remicade®	TBD; BLA submitted	RA, AS, PsO, PsA, CD, UC
Ranibizumab (Santo)	Lucentis®	TBD; BLA submitted	Wet AMD
Rituximab (Amgen)	Rituxan®	TBD; BLA submitted	RA, CLL, NHL (indolent), antineutrophil cytoplasmic antibody-associated vasculitis
Rituximab (Pfizer)	Rituxan®	TBD; BLA submitted	RA, CLL, NHL (indolent), antineutrophil cytoplasmic antibody-associated vasculitis
Teriparatide recombinant human (Pfenex)	Forteo®	TBD; BLA submitted	Osteoporosis, osteopenia

**Follow-on insulin products*

Abbreviations: AMD=age-related macular degeneration, AML=acute myeloid leukemia, AS=ankylosing spondylitis, BLA=biologics license application, CD=Crohn's disease, CKD=chronic kidney disease, CLL=chronic lymphocytic leukemia, CRC=colorectal cancer, CRL = complete response letter, HS=hidradenitis suppurativa, HSARS=hematopoietic syndrome of acute radiation syndrome, JIA=juvenile idiopathic arthritis, NHL=non-Hodgkin's lymphoma, NSCLC=non-small cell lung cancer, PsA=psoriatic arthritis, PsO=plaque psoriasis, Q3=third quarter, RA=rheumatoid arthritis, RCC=renal cell carcinoma, T1DM=type 1 diabetes mellitus, T2DM=type 2 diabetes mellitus, TBD=to be determined, UC=ulcerative colitis

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INDICATIONS

Adult Ulcerative Colitis (UC)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for inducing and maintaining clinical response, inducing and maintaining clinical remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission.

Adult Crohn's Disease (CD)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for achieving clinical response, achieving clinical remission, and achieving corticosteroid-free remission.

IMPORTANT SAFETY INFORMATION

- ENTYVIO (vedolizumab) for injection is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.
- Infusion-related reactions and hypersensitivity reactions including anaphylaxis have occurred. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.
- Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.

In UC & CD

FOR ADULTS WITH MODERATELY TO SEVERELY ACTIVE UC OR CD FOR WHOM OTHER THERAPIES HAVE NOT WORKED WELL ENOUGH

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vedolizumab

Long-term focus—from the start:

GI-FOCUSED ACTION

Entyvio specifically binds to α4β7 integrin, blocking its interaction with MAdCAM-1, which is mainly expressed on gut endothelial cells[1]

WITH

REMISSION ACHIEVED

UC and CD patients achieved remission at 52 weeks vs placebo. Studies included bio-naïve and anti-TNFα–experienced patients[1,2]

AND

5-YEAR INTEGRATED SAFETY

A 5-year analysis, including an open-label continuation study, demonstrated consistent results with clinical trials across safety parameters[1,3]

Individual results may vary.

Begin the Change

IMPORTANT SAFETY INFORMATION *(continued)*

- Although no cases of PML have been observed in ENTYVIO clinical trials, JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.
- Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.
- Most common adverse reactions (incidence ≥3% and ≥1% higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

Please see brief summary of Prescribing Information on adjacent pages.

References: 1. Entyvio [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc. **2.** Data on file. Takeda Pharmaceuticals America, Inc. Deerfield, IL. **3.** Colombel JF, et al. *Gut*. 2017;66:839-851.

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Takeda

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ENTYVIO (vedolizumab) for injection, for intravenous use

INDICATIONS AND USAGE

Adult Ulcerative Colitis

ENTYVIO (vedolizumab) is indicated for:

- inducing and maintaining clinical response,
- inducing and maintaining clinical remission,
- improving the endoscopic appearance of the mucosa, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Adult Crohn's Disease

ENTYVIO (vedolizumab) is indicated for:

- achieving clinical response,
- achieving clinical remission, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate) *[see Warnings and Precautions and Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions and Hypersensitivity Reactions

In UC Trials I and II and CD Trials I and III, hypersensitivity reactions occurred including a case of anaphylaxis (one out of 1434 patients [0.07%]) *[see Adverse Reactions]*. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. The majority were mild to moderate in severity as assessed by the investigator. Experience with other biologic medications suggests that hypersensitivity reactions and anaphylaxis to ENTYVIO may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion.

If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment (e.g., epinephrine and antihistamines).

Infections

Patients treated with ENTYVIO are at increased risk for developing infections *[see Adverse Reactions]*. The most commonly reported infections in clinical trials occurring at a rate greater on ENTYVIO than placebo involved the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection). Serious infections have also been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding treatment in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution when considering the use of ENTYVIO in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice. For progressive multifocal leukoencephalopathy (PML), see *Warnings and Precautions*.

Progressive Multifocal Leukoencephalopathy

Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS). PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised.

In ENTYVIO clinical trials, patients were actively monitored for PML with frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. While zero cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out. No claims of comparative safety to other integrin receptor antagonists can be made based on this data.

Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue dosing permanently.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury *[see Adverse Reactions]*.

Live and Oral Vaccines

Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following topics are also discussed in detail in the Warnings and Precautions section:

- Infusion-Related Reactions and Hypersensitivity Reactions *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions]*
- Liver Injury *[see Warnings and Precautions]*

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 the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to ENTYVIO in 3,326 patients and healthy volunteers in clinical trials, including 1,396 exposed for greater than one year, and 835 exposed for greater than two years.

The safety data described in *Table 2* are derived from four controlled Phase 3 trials (UC Trials I and II, and CD Trials I and III); data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

In these trials, 1,434 patients received ENTYVIO 300 mg for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis and 962 patients had Crohn's disease. Patients were exposed for a mean duration of 259 days (UC Trials I and II) and 247 days (CD Trials I and III).

Adverse reactions were reported in 52% of patients treated with ENTYVIO and 45% of patients treated with placebo (UC Trials I and II: 49% with ENTYVIO and 37% with placebo; CD Trials I and III: 55% with ENTYVIO and 47% with placebo). Serious adverse reactions were reported in 7% of patients treated with ENTYVIO compared to 4% of patients treated with placebo (UC Trials I and II: 8% with ENTYVIO and 7% with placebo; CD Trials I and III: 12% with ENTYVIO and 9%, with placebo).

The most common adverse reactions (reported by ≥3% of patients treated with ENTYVIO in the UC Trials I and II and CD Trials I and III combined group and ≥1% higher than in combined placebo group) were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain and pain in extremities (*Table 2*).

Table 2. Adverse Reactions in ≥3% of ENTYVIO-treated Patients and ≥1% Higher than in Placebo (UC Trials I and II* and CD Trials I and III*)

Adverse Reaction	ENTYVIO† (N=1434)	Placebo‡ (N=297)
Nasopharyngitis	13%	7%
Headache	12%	11%
Arthralgia	12%	10%
Nausea	9%	8%
Pyrexia	9%	7%
Upper respiratory tract infection	7%	6%
Fatigue	6%	3%
Cough	5%	3%
Bronchitis	4%	3%
Influenza	4%	2%
Back pain	4%	3%
Rash	3%	2%
Pruritus	3%	1%
Sinusitis	3%	1%
Oropharyngeal pain	3%	1%
Pain in extremities	3%	1%

*Data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

†Patients who received ENTYVIO for up to 52 weeks.

‡Patients who received placebo for up to 52 weeks.

Safety data for patients (n=279) in UC Trials I and II and CD Trials I and III who received ENTYVIO at Weeks 0 and 2 and were then randomized to placebo at Week 6 for up to 52 weeks, and for patients (n=416) in CD Trial II, a 10 week Crohn's disease trial, are similar to those listed in *Table 2*.

Infusion-Related Reactions and Hypersensitivity Reactions

Serious infusion-related reactions and hypersensitivity reactions including anaphylaxis have been reported following ENTYVIO administration in clinical trials *[see Warnings and Precautions]*. In UC Trials I and II and Crohn's Trials I and III, one case of anaphylaxis [one out of 1434 patients treated with ENTYVIO (0.07%)] was reported by a Crohn's disease patient during the second infusion (symptoms reported were dyspnea, bronchospasm, urticaria, flushing, rash and increased blood pressure and heart rate) and was managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone.

In UC Trials I and II and CD Trials I and III, 4% of patients treated with ENTYVIO and 3% of patients treated with placebo experienced an infusion-related reaction (IRR). The most frequently observed IRR in the patients treated with ENTYVIO (reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria and vomiting (each of these adverse reactions occurred in <1% in all patients treated with ENTYVIO) and no individual adverse reaction reported occurred at a rate above 1%. These reactions generally occurred within the first two hours after the infusion and resolved with no treatment or following antihistamine and/or IV hydrocortisone treatment. Less than 1% of patients treated with ENTYVIO had IRRs assessed by the investigator as severe, and IRRs requiring discontinuation of study treatment occurred in <1%.

In clinical trials, for patients with mild IRRs or hypersensitivity reactions, physicians were allowed to pretreat with standard medical treatment (e.g., antihistamine, hydrocortisone and/or acetaminophen) prior to next infusion.

Infections

In UC Trials I and II and CD Trials I and III, the rate of infections was 0.85 per patient-year in the patients treated with ENTYVIO and 0.7 per patient-year in the patients treated with placebo *[see Warnings and Precautions]*. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of patients discontinued ENTYVIO due to infections.

In UC Trials I and II and CD Trials I and III, the rate of serious infections was 0.07 per patient-year in patients treated with ENTYVIO and 0.06 per patient-year in patients treated with placebo. Serious infections were more common in Crohn's disease patients than ulcerative colitis patients, and anal abscesses were the most frequently reported serious adverse reaction in Crohn's disease patients. Over 48 months, there was no increase in the rate of serious infections.

In controlled- and open-label long-term extension trials in adults treated with ENTYVIO, serious infections have been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

In UC Trials I and II and CD Trials I and III, sepsis, including bacterial sepsis and septic shock, was reported in four of 1434 (0.3%) patients treated with ENTYVIO and in two of 297 patients treated with placebo (0.7%). During these trials, two Crohn's disease patients treated with ENTYVIO died due to reported sepsis or septic shock; both of these patients had significant comorbidities and a complicated hospital course that contributed to the deaths. In an open label long-term extension trial, additional cases of sepsis (some fatal), including bacterial sepsis and septic shock, were reported. The rate of sepsis in patients with ulcerative colitis or Crohn's disease receiving ENTYVIO was two per 1000 patient-years.

In clinical trials, all patients were screened for tuberculosis. One case of latent, pulmonary tuberculosis was diagnosed during the controlled trials with ENTYVIO. Additional cases of pulmonary tuberculosis were diagnosed during the open-label trial. All of these observed cases occurred outside the United States, and none of the patients had extrapulmonary manifestations.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO *[see Warnings and Precautions]*. In UC Trials I and II and CD Trials I and III, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five ENTYVIO doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled trials, the incidence of ALT and AST elevations ≥3 x ULN was <2% in patients treated with ENTYVIO and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

Malignancies

In UC Trials I and II and CD Trials I and III, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1434 (0.4%) patients treated with ENTYVIO, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), carcinoid tumor of the appendix (n=1) and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).

Malignancies (excluding dysplasia and basal cell carcinoma) observed during the ongoing open-label long-term extension trial included B-cell lymphoma, breast cancer, colon cancer, malignant hepatic neoplasm, malignant lung neoplasm, malignant melanoma, lung cancer of primary neuroendocrine carcinoma, renal cancer and squamous cell carcinoma. Overall, the number of malignancies in the clinical trials was small; however, long-term exposure was limited.

Live and Oral Vaccines

There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO.

In a placebo-controlled study of healthy volunteers, 61 subjects were given a single ENTYVIO 750 mg dose (2.5 times the recommended dose), and 62 subjects received placebo followed by intramuscular vaccination with Hepatitis B surface antigen and oral cholera vaccine. After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with ENTYVIO did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to ENTYVIO did have lower seroconversion rates and anti-cholera titers relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to vedolizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In UC Trials I and II and CD Trials I and III, in patients who received ENTYVIO, the frequency of antibodies detected in patients was 13% at 24 weeks after the last dose of study drug (greater than five half-lives after last dose). During treatment, 56 of 1434 (4%) of patients treated with ENTYVIO had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. Nine of 56 patients were persistently positive (at two or more study visits) for anti-vedolizumab antibody and 33 of 56 patients developed neutralizing antibodies to vedolizumab. Among eight of these nine subjects

with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations. None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52 in the controlled trials.

DRUG INTERACTIONS

Natalizumab

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab.

TNF Blockers

Because of the potential for increased risk of infections, avoid the concomitant use of ENTYVIO with TNF blockers.

Live Vaccines

Live vaccines may be administered concurrently with ENTYVIO only if the benefits outweigh the risks *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENTYVIO during pregnancy. Information about the registry can be obtained by calling 1-877-TAKEDA7 (1-877-825-3327).

Pregnancy Category B:

Risk Summary

There are no studies with ENTYVIO in pregnant women. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels 20 times the recommended human dosage. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefits to the mother outweigh the risk to the unborn child.

Clinical Considerations

Any adverse pregnancy effect from ENTYVIO would likely be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data

A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage).

Nursing Mothers

It is unknown whether vedolizumab is present in human milk. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman.

Pediatric Use

Safety and effectiveness of ENTYVIO in pediatric patients have not been established.

Geriatric Use

Clinical trials of ENTYVIO did not include sufficient numbers of subjects aged 65 and over (46 Crohn's and ulcerative colitis patients aged 65 and over were treated with ENTYVIO during controlled Phase 3 trials) to determine whether they respond differently from younger subjects. However, no overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Manufactured by:
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For more information, go to www.ENTYVIO.com or call 1-877-825-3327

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High-Cost Therapies

Current Trends and Innovative Payment Strategies

The high cost of prescription drugs is a problem that continues to challenge the healthcare system in the U.S., with growth in prescription drug expenditures projected to outpace overall healthcare spend.[1] According to the Office of the Assistant Secretary for Planning and Evaluation, prescription drug spending in the U.S. reached $457 billion in 2015, or 16.7% of the overall spend on personal healthcare services. Of the total prescription drug spend in 2015, approximately 72% ($328 billion) went toward retail drugs, or those dispensed at a pharmacy, and 28% ($128 billion) was spent on nonretail drugs, or those administered directly to a patient by a healthcare provider.[1]

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A key driver of the mounting drug spend is the increased use and cost of specialty drugs.[1] Recent scientific advancements have led to highly targeted, increasingly effective medications that have the potential to treat, and in some cases cure, a broad range of serious and life-threatening conditions.[2] Many of these medications coming to market may offer significant medical innovation for a relatively small patient population at a high cost.[2]

What makes a medication a specialty drug compared to a traditional drug? Although different health plans may use slightly different definitions, 85% agree that high cost is a key factor in identifying specialty drugs.[3] Other factors that may be considered in classifying a drug as specialty or traditional include special storage requirements, dosage and administration requirements (e.g., injection, infusion, etc.), specific handling instructions, or more intensive patient monitoring programs.[4,5]

One source defines a specialty drug as a product used for the treatment of a chronic, complex, or rare disease that meets at least four of the following criteria:[5]

1. Cannot be self-administered
2. Special patient monitoring, counseling, or Risk Evaluation and Mitigation Strategies program requirements
3. Treatment is initiated by a specialist
4. Special handling requirements or a unique and/or narrow distribution network
5. Cost exceeds $6,000 per year
6. Reimbursement assistance is required

The Centers for Medicare & Medicaid Services (CMS) uses a cost threshold of $600 or more per month, or $7,200 annually, to classify drugs as specialty.[3] Many specialty drugs coming to market can exceed an annual cost of $100,000 per patient.[3] According to a report from the AARP Public Policy Institute, the

average cost of treatment with a single specialty drug in 2015 was $52,486, which represents an increase of almost $35,000 from 2006.[6] The use of specialty drugs is also increasing. In 2015, the utilization of such medications increased by 6.8% due to an increased use of existing agents as well as the introduction of new specialty drugs.[3] There is also a greater focus on the development of these products; as of 2017, more than 900 specialty drugs were reported to be in development. In 2017, 21 of the 42 new chemical entities that were approved by the U.S. Food and Drug Administration (FDA) were for the treatment of rare diseases and 14 were approved for the treatment of cancer, two specialty drug therapeutic areas that are associated with very high price tags.[5]

While biologic products are typically what we think of when we think about high-cost specialty medications, we are now seeing significant development efforts in the field of cell and gene therapy.

Current Trends in Cost-Management Strategies

Given the increasing cost and use of these medications, specialty drug spend is outpacing traditional drug spend. As of 2017, specialty accounted for more than 43% of the total drug spend in the U.S.[5] Now more than ever, it is crucial for payors to develop innovative management strategies to contain these rising costs and ensure that potentially life-saving medications are available to the patients who need them. Some strategies currently being employed by payors in both private and public plans include negotiating rebates with manufacturers, formulary management and cost sharing, step therapy, and prior authorization.[3]

Although there are several possible approaches for negotiating rebate agreements, at a high level, payors may offer a manufacturer preferred placement on their formulary in exchange for a reduced net price. This strategy may help the payor reduce expenditures within a medication class while helping the manufacturer secure an advantage over competitors.[3] Payors also frequently use formulary management and cost-sharing strategies to reduce their costs. In general, specialty drugs are placed at the highest formulary tier, which correlates with greater cost sharing from the patient (i.e., higher out-of-pocket costs). Increasing the amount paid by the patient may save the payor some money. However, it may also discourage patients from using necessary medications if their out-of-pocket costs are too high. This could potentially lead to poorer outcomes if their disease is being inadequately managed.[3] To avoid such an unintended consequence, payors and manufacturers may consider arrangements where additional rebates are granted if the payor allows the patient to have lower out-of-pocket costs. This scenario would lower the costs for payors and patients alike, and would avoid discouraging medication adherence.[3]

Step therapy is another important strategy used by payors to lower plan costs. With this approach, payors may require patients to try and fail treatment with less costly alternatives before moving on to more expensive therapies.[3] Similarly, prior authorizations may be put in place, requiring a prescriber to document that a given medication is medically necessary and clinically appropriate for the patient prior to granting coverage. Prior authorization is also an important tool that can be used to ensure that specialty medications are being used appropriately, given their complex dosing and administration requirements.[3]

More Work to Be Done

Using strategies such as those discussed above, payors have managed to slow drug spend growth, taking into account discounts and rebates from manufacturers. In fact, the net drug spend for all types of medications grew by just 0.6% in 2017 after discounts and rebates.[5] Looking specifically at retail and mail order pharmacy dispensing, the net drug spend actually declined by 2.1%.[5] A report from IQVIA projects that there will be 2% to 5% net growth in drug spend through 2022, which will be largely driven by the number of new medications, including specialty and orphan drugs.[5] It is important to note that the net growth is being offset to some degree by the loss of brand exclusivity that will occur over that same time period for other medications.[5] Significant progress has been made in curtailing the growth of net drug spend; however, the number of high-cost medications that continue to come to market each year highlights the need for innovative payment models to help sustain this pace of rapid medical innovation.

While biologic products are typically what we think of as high-cost specialty medications, we are now seeing significant development efforts in the field of cell and gene therapy. In late 2017, the FDA approved the first chimeric antigen receptor (CAR)-T cell therapies, including tisagenlecleucel (Kymriah®, Novartis) for the treatment of patients 25 years of age and younger with B-cell precursor acute lymphoblastic leukemia, and axicabtagene ciloleucel (Yescarta®, Kite Pharma/Gilead) for the treatment of adults with large B-cell lymphoma.[7-9] The FDA also recently granted tisagenlecleucel approval for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after

two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.[8] These cell therapies are very complex and require the ex vivo modification of a patient's own cells to express the CAR protein, and those cells are then reinfused into the patient where they target and attack cancer cells.[7] Although these CAR-T therapies came to market with hefty price tags of $475,000 and $373,000 per patient for tisagenlecleucel and axicabtagene ciloleucel, respectively, a report from the Institute for Clinical and Economic Review found that the cost of these products is aligned with the clinical benefit they provide for patients who have failed essentially all other treatment options.[10]

Subsequently, in December 2017, the FDA approved the first gene therapy, voretigene neparvovec (Luxturna™, Spark Therapeutics), for the treatment of patients with biallelic RPE65-mediated retinal dystrophy.[11] Voretigene neparvovec offers a potential cure for hereditary blindness that is given as a single subretinal injection to each eye. In January 2018, Spark Therapeutics announced that voretigene neparvovec would cost $425,000 per eye, or a total of $850,000 for both eyes, bringing the conversation about alternative payment models into the spotlight.[11,12]

While manufacturers have seemingly tiptoed around an unspoken $1 million threshold for new orphan drugs in recent years, it appears that we may soon surpass that milestone. Analysts at Leerink predict that gene therapies in late-stage development for the treatment of hemophilia may come to market costing $1.5 million or more.[13] Hemophilia is a disease historically managed with on-demand or prophylactic therapy using factor replacement products, and could be associated with medication costs between $580,000 and $800,000 annually.[13,14] For more difficult to treat patients, such as those who develop inhibitors, annual treatment costs could approach $1 million. FDA approval of gene therapies that could potentially cure hemophilia with one-time administration of a replacement gene could transform hemophilia from a costly chronic disease to one that could be easily cured — for a price.[13,14] Given the high cost and one-time administration of such gene therapies, the payment structure will almost certainly need to be reevaluated, as payors are left wondering how they will balance the long-term clinical benefit and cost savings with the significant up-front cost.

In addition to the high up-front cost of gene therapy, there are several other challenges associated with these products that payors face, including small populations of patients who may be eligible for treatment, narrow treatment windows, a lack of long-term safety and efficacy data, and other costs associated with the administration of gene therapy.

Innovative Pricing Models

In addition to the high up-front cost of gene therapy, there are several other challenges associated with these products that payors face, including small populations of patients who may be eligible for treatment, narrow treatment windows, a lack of long-term safety and efficacy data, and other costs associated with the administration of gene therapy, such as hospitalizations.[2]

ANNUITY PAYMENT MODEL

Under the annuity payment approach, payors and manufacturers would agree to a payment schedule consisting of planned payments over a period of time rather than a one-time, up-front cost. Depending on the disease state and/or the drug, the terms of the agreement could be negotiated such that payments would be made over several months or even several years.[2] For example, gene therapy costing $1.5 million that may potentially cure hemophilia could have payments spread out over the course of several years. This payment model is one of the most commonly discussed approaches for managing high-cost drugs and has reportedly been under consideration by Spark Therapeutics, the manufacturer of voretigene neparvovec, to help ensure access for those who could benefit from treatment.[15]

As with many payment models, there are risks that would need to be considered. For example, a payor may agree to take on several years' worth of payments for a hemophilia gene therapy, given the cost savings they hope to achieve when they no longer have to pay for factor replacement if that patient is cured.[2] It is possible that the member could subsequently switch insurance plans after receiving the curative gene therapy, leaving the initial payor with the bill and the new payor with the cost savings. Other concerns with this payment model include the potential impact of the extended

payment schedule on government reporting of drug prices and how it will impact Medicaid best price, which is discussed further below.[2]

OUTCOMES-BASED PAYMENT MODEL

As the name suggests, outcomes-based payment models are agreements in which payment is contingent on certain clinical outcomes being achieved at certain points in time.[2] This type of agreement is particularly appealing to payors for therapies that may have limited safety or efficacy data, or for therapies lacking long-term data. This approach helps spread the risk among payors and manufacturers; however, it is likely that payors would still be responsible for any hospital expenses incurred during administration of the therapy, or for the treatment of side effects associated with the therapy.[2]

In September 2017, it was announced that Novartis was working with CMS to establish an outcomes-based contract for tisagenlecleucel for the treatment of children and young adults with B-cell precursor acute lymphoblastic leukemia.[16] Under this agreement, CMS would only pay for tisagenlecleucel if the patient demonstrated a response to therapy by the end of the first month following treatment. In July 2018, it was announced that this payment deal was suspended; however, CMS has said it will not discard value-based approaches.[17] Novartis is reportedly also working with private payors to reach similar agreements for tisagenlecleucel, and is seeking opportunities to develop similar arrangements for other medications.[16]

INDICATION-BASED PRICING

The concept of indication-based pricing has also recently come into the spotlight, as tisagenlecleucel received FDA approval in May 2018 for its second indication: treatment of adults with large B-cell lymphoma.[8] As previously noted, tisagenlecleucel initially came to market at a higher price than axicabtagene ciloleucel, another CAR-T therapy, which was largely due to the fact that the initial treatment pool for tisagenlecleucel was much smaller than that for axicabtagene ciloleucel. With the approval of the second indication, tisagenlecleucel would potentially compete with axicabtagene ciloleucel for the same treatment pool.[18] Following FDA approval for the second indication, Novartis announced that it would establish an indication-based price of $373,000 for tisagenlecleucel for the treatment of large B-cell lymphoma, in line with the list price for its competitor.[19] Use of indication-based pricing models may allow manufacturers to set a price that aligns more closely with the clinical value that a therapy provides for each disease it is approved to treat.[16]

When considering outcomes-based agreements, the time at which the outcome is evaluated should be consistent with when the outcome would be reasonably expected to occur.

Challenges and Future Directions

Another challenge unique to outcomes-based pricing is associated with the establishment and tracking of appropriate outcomes. Depending on the therapy and disease state under consideration, the outcomes could be difficult to track or, in some cases, subjective and based on patient reporting. When considering outcomes-based agreements, payors and manufacturers should ensure that they select clinically appropriate outcomes based on the disease state and the clinical outcome that is being outlined in the contract. In addition, the time at which the outcome is evaluated should be consistent with when the outcome would be reasonably expected to occur. The outcomes data should also be collected in a timely manner, in the event that the patient treated is lost to follow-up or switches insurance plans, at which time the data may not be available to the payor. It is crucial for payors to take into consideration the quality of the data that they have available to them and the time frame in which it becomes available. For example, if an outcome should be measured one month post-treatment and the medical claims data is either not available at that time or of a poor quality, the payor may consider outreach to the provider who administered the treatment to inquire about treatment success. In such situations, it will be imperative to have provider buy-in to ensure that payors are able to obtain the necessary information.

The payment models discussed above present some unique challenges and important opportunities. Payors and manufacturers alike will need to continue to think outside the box when developing innovative payment models to ensure that payment structures can keep pace with medical innovation.

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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.

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

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Cystic Fibrosis

Moving Toward More Personalized Care

Cystic fibrosis (CF) is a fatal genetic disease caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leading to airway obstruction with recurrent inflammation and infection.[1] Approximately 30,000 individuals in the U.S. have CF, most of whom are diagnosed within the first six months of life.[2] CF is autosomal recessive, as only one functioning allele of the CFTR gene is required to prevent CF. When both alleles are defective, neither can produce functional CFTR protein. One in 30 Caucasian Americans and roughly 4% of individuals of European descent are carriers of a cystic fibrosis mutation.[3]

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The most common CFTR mutation — a ΔF508 deletion — is present in 90% of CF cases in the U.S. and around two-thirds of CF cases (homozygous or heterozygous) worldwide.[4]

Cell culture studies have shown that CFTR defects in the endoplasmic reticulum can be "corrected" through the application of certain small-molecule modulators and, once at the surface, suboptimal channel functioning of the major mutant can be "potentiated" pharmacologically.[1] Due to early provision of care in specialized reference centers and more comprehensive care of CF, survival has improved over time.[5] Unfortunately, despite significant advances in supportive care and our understanding of CF pathophysiology, there is still no cure for the disease.

TREATMENT

GUIDELINES

At this time, there are several guidelines available to guide the effective identification and management of CF over time. The most comprehensive group of guidelines has been set forth by the Cystic Fibrosis Foundation (CFF) and includes recommendations in the following areas:[6]

1. Diagnostic care
2. Nutrition and gastrointestinal (GI) care
3. Respiratory care
4. Infection prevention and control
5. Age-specific care
6. Other CF-related conditions
7. Screening and treating depression/anxiety
8. CFTR modulator therapy

GOALS OF THERAPY

While there is currently no cure for CF, treatment can ease symptoms and reduce complications. Early, aggressive intervention and close monitoring is recommended in order to achieve the most personalized approach to care. The overall goals of CF treatment are to:[7]

1. Prevent and control lung infections
2. Loosen and remove mucus from the lungs
3. Prevent and treat intestinal blockage
4. Provide adequate nutrition

To help achieve these goals, there are several agents that are commonly used to manage the symptoms of CF. They include:[7]

1. Antibiotics to manage (and prevent) lung infections
2. Mucus-thinning drugs to help improve lung function
3. Bronchodilators to relax the muscles around the bronchial tubes and keep the airways open
4. Oral pancreatic enzymes to help digestive absorption
5. Anti-inflammatory agents
6. Agents to treat associated conditions or complications, such as insulin for diabetes and bisphosphonates for osteoporosis
7. Agents devised to potentially reverse abnormalities in chloride transport (e.g., ivacaftor, lumacaftor, tezacaftor)
8. Multivitamins

CURRENT TREATMENT STRATEGIES

Wide-ranging CF research has resulted in significant improvements in treatment, nearly quadrupling the median life expectancy in the U.S.[8] Another way to look at this is Median Predicted Survival Age. The 2016 data from the Cystic Fibrosis Data Registry Report states the median survival of those born in 2016 was 47.7 years as compared to 41.2 years in 2015.[8] On the flip side, from the same Registry Report, the median age of death was 29.6 years in 2016.[8] The improved clinical status of CF patients is primarily the result of increased understanding of the natural course of infection and inflammation in CF, which has effectively led to implementation of strategies to increase the life expectancy and quality of life of CF patients.[9] These strategies are multifold and include:[9]

1. Early diagnosis
2. Timely and aggressive nutritional guidance
3. Augmentation of mucociliary clearance and improved drainage
4. Prompt initiation of antimicrobial and anti-inflammatory therapy
5. Management of exacerbations
6. Effective hygienic measures in and outside CF centers
7. Identification and treatment of complications

While substantial progress has been made in the treatment of CF, it still carries a significant burden in terms of symptoms, requirement for treatment, and early mortality.[10] Treatment of patients with CF has been transformed by the availability of agents that actually target the basic chloride defect in the disease. This embodies the goal of precision medicine, which encompasses preventive and therapeutic strategies and considers differences among individuals.[11] The entirety of CF care, from diagnosis to understanding the clinical phenotype and developing a therapeutic strategy, depends on considering individual characteristics to achieve optimal outcomes.[11]

In recent years, several improved treatment options have come to the forefront. For example, several agents that correct the malfunctioning protein made by the CFTR gene have been released in the past decade. Mechanical chest physical therapy devices can help loosen chest mucus while lung transplantation has become an option for some people with CF who have sustained severe lung damage. Digestive problems can be managed with nutritional therapy, oral pancreatic enzymes, and medications to reduce stomach acid. Other nonpharmacologic treatment methods include pulmonary rehabilitation, surgical procedures, oxygen therapy, and feeding tubes. Table 1 lists several classes and individual agents that may be used to treat CF.

The management of CF has improved significantly over the past 50 years, and while infants born with CF many years ago would have been unlikely to live past one year, CF patients today are likely to live well into adulthood.[8] Significant advances in CF treatment

TABLE 1. AGENTS/PREPARATIONS APPROVED OR COMMONLY USED FOR CF AND RELATED SEQUELAE*

Class	Examples	Purpose
Antibiotics	Amoxicillin and clavulanic acid (Augmentin®) Azithromycin Aztreonam (Cayston®) Cefuroxime Cephalexin Quinolones Sulfamethoxazole and trimethoprim (Bactrim®) Tobramycin Others (several)	Fight infections caused by bacteria in CF patients.
Bronchodilators	Albuterol (Proventil®) Salmeterol (Serevent®) (rarely used alone) Terbutaline Others (several)	Relax airway muscles; assist with coughing up mucus.
CFTR Modulators	Ivacaftor (Kalydeco®) Lumacaftor/ivacaftor (Orkambi®) Tezacaftor/ivacaftor (Symdeko™)	Correct the malfunctioning protein made by the CFTR gene.
Mucosal Thinners	Hypertonic saline Dornase alfa (Pulmozyme®)	Thin the mucus in the airways; enhance coughing for mucus removal.
Nutritional/GI/Other	AquADEKs Pancrelipase enzyme products Relizorb™	Vitamin and enzyme preparations designed as supplements for CF patients.

**Adapted from CFF: http://www.cff.org/Life-With-CF/Treatments-and-Therapies*

have led to more fulfilling lives for patients, as well as friends and families. The cornerstones of treatment are management and prevention of airway infection, along with good nutrition and an active lifestyle. Due to the wide variation in CF symptoms, treatment most often occurs at specialist centers and is personalized to each individual patient.

Historically, treatment modalities for CF lung disease have primarily targeted the downstream effects of a dysfunctional CFTR protein. The discovery of the CFTR gene in 1989 led to a more sophisticated understanding of the genetic component of CF, and much progress has been made over the past decade with the development of orally bioavailable drugs that target defective CFTR proteins caused by specific mutations.

The recent approvals of ivacaftor, lumacaftor, tezacaftor, and combination therapies represent a new era of precision medicine. The newer CFTR modulators target the basic defect in CF and offer the hope of improved treatment options for many more people with CF. The novelty of approved and investigational agents targeting the basic defect underlying CF is that they are mutation-specific. Table 2 lists the indications for the currently available, Food and Drug Administration (FDA)-approved CFTR modulators.

There are approximately 2,000 known mutations in the CFTR gene.[12] Table 3 lists the CFTR gene mutations that produce CFTR protein and are responsive to ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor, respectively.

TABLE 2. FDA-APPROVED INDICATIONS FOR CURRENTLY AVAILABLE CFTR MODULATORS

Drug Name	Patient Age Groups	Mutations
Ivacaftor (Kalydeco®)	2 years and older	Patients who have at least one mutation in their CF gene that is responsive to ivacaftor. There are 38 mutations that are responsive to ivacaftor based on a positive clinical response and/or in vitro data.
Lumacaftor/ivacaftor (Orkambi®)	6 years and older	Patients who are homozygous for the ΔF508del mutation.
Tezacaftor/ivacaftor (Symdeko™)	12 years and older	Patients who are homozygous for the ΔF508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor. There are 27 mutations that are responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.

NOVEL/EMERGING THERAPIES AND FUTURE DIRECTIONS

RECENTLY APPROVED THERAPY

In February 2018, the FDA approved tezacaftor/ivacaftor (Symdeko™, Vertex) for the treatment of CF in patients ages 12 and older who have two copies of the ΔF508del mutation in the CFTR gene or who have at least one mutation that is responsive to tezacaftor/ivacaftor.[12] The tezacaftor component addresses the trafficking and processing defect of the CFTR protein to enable it to reach the cell surface, whereas ivacaftor works to increase the amount of time the protein can stay open.[12] Two phase III trials — EVOLVE and EXPAND — evaluated the safety and efficacy of tezacaftor/ivacaftor in patients 12 years and older who have CF and two copies of the ΔF508del mutation or one ΔF508del mutation and one mutation that results in residual CFTR function.[12] In both studies, patients treated with tezacaftor/ivacaftor experienced statistically significant and clinically meaningful improvements in lung function and other measures of disease.[12] Preliminary data from the ongoing EXTEND rollover study demonstrate that the lung function improvements and the safety and tolerability profiles observed in EVOLVE and EXPAND were sustained for up to 48 total weeks of tezacaftor/ivacaftor treatment.[12]

EMERGING THERAPIES

While CFTR-directed therapy has the highest potential to improve patient outcomes, it is important to continue to seek additional treatment options for all aspects and symptoms of CF lung disease.[13] These may include modifiers of ion channels other than CFTR, such as activators of alternative chloride channels or inhibitors of sodium absorption. Several compounds in development aim to correct these defects directly. Aside from this, there are a number of agents in phase II and III trials focusing on symptomatic CF treatment, including mucociliary clearance, inflammation, infection, and nutritional aspects of care. Table 4 lists various therapies in phase II and III development, including investigational treatments that restore CFTR function, improve mucociliary clearance, and reduce inflammation.

The discovery of the CFTR gene in 1989 led to a more sophisticated understanding of the genetic component of CF, and much progress has been made over the past decade with the development of orally bioavailable drugs that target defective CFTR proteins caused by specific mutations.

TABLE 3. LIST OF CFTR GENE MUTATIONS THAT PRODUCE CFTR PROTEIN AND ARE RESPONSIVE TO CFTR MODULATORS

	Lumacaftor/Ivacaftor (Orkambi®)	Tezacaftor/Ivacaftor (Symdeko™)	Ivacaftor (Kalydeco®)
ΔF508del (two copies)	✓	✓	
E56K		✓	✓
G178R		✓	✓
P67L		✓	✓
G551D		✓	✓
R74W		✓	✓
G551S		✓	✓
D110E		✓	✓
G1244E		✓	✓
D110H		✓	✓
G1349D		✓	✓
R117C		✓	✓
R117H		✓	✓
E193K		✓	✓
S549N		✓	✓
L206W		✓	✓
S549R		✓	✓
R347H		✓	✓
S1251N		✓	✓
R352Q		✓	✓
S1255P		✓	✓
A455E		✓	✓
G1069R		✓	✓
D579G		✓	✓
R1070Q		✓	✓
711+3A→G		✓	✓
E831X			✓
S945L			✓
S977F			✓
F1052V			✓
K1060T			✓
A1067T			✓
R1070W			✓
F1074L			✓
D1152H			✓
D1270N			✓
2789+5G→A			✓
3272-26A→G			✓
3849+10kbC→T			✓

TRIPLE-THERAPY COMBINATIONS

Two triple-therapy combinations that utilize a tezacaftor/ivacaftor (Symdeko™, Vertex) backbone and an additional investigational transmembrane regulator corrector are in development: Vertex's VX-445/tezacaftor/ivacaftor and VX-659/tezacaftor/ivacaftor. Two separate phase III studies of VX-445/tezacaftor/ivacaftor and VX-659/tezacaftor/ivacaftor are underway in patients ages 12 and older; studies are being conducted for each triple-therapy combination in patients who have one ΔF508del mutation and one minimal function mutation not likely to respond to tezacaftor and/or ivacaftor.[13] In the phase II trials combining ivacaftor and tezacaftor with each of the investigational agents, the highest tested dose of VX-659 led to a 13.3% forced expiratory volume in one second (FEV1) improvement, and the highest tested dose of VX-445 showed a 13.8% FEV1 improvement, both of which were deemed to be statistically significant.[14] The first phase III trial of VX-659/tezacaftor/ivacaftor has begun, and the manufacturer has announced that it hopes to begin phase III testing with VX-445/tezacaftor/ivacaftor later this year.[15]

As of April 2018, there are more than 200 currently eligible minimal function CFTR mutations for the VX-659 or VX-445 phase III studies.[16]

OTHER EMERGING AREAS

There is also a good deal of optimism surrounding the prospect of gene replacement or editing to correct mutations in CF; however, these investigational treatments have not yet been studied in humans, and data regarding their safety and efficacy will likely be unavailable for several years.

Treatment advances, while exciting, have presented managed care organizations with the challenge of finding ways to pay for these important therapies. Mean annual per-patient healthcare costs for treating CF in the U.S. are $15,571, with costs for mild, moderate, and severe disease listed at $10,151, $25,647, and $33,691, respectively.[17]

TABLE 4. CF PIPELINE AGENTS/PREPARATIONS CURRENTLY IN PHASE II OR III*

Purpose	Phase II	Phase III
Restore CFTR Function	QBW251 FDL169 GLPG2222 PTI-428 VX-561	VX-445/tezacaftor/ivacaftor VX-659/tezacaftor/ivacaftor
Mucociliary Clearance	OligoG QBW276 SPX-101	None
Anti-Inflammatory	Lenabasum (JBT-101) Acebilustat (CTX-4430) LAU-7b	None

**Adapted from CFF: http://www.cff.org/trials/pipeline*

There is also a good deal of optimism surrounding the prospect of gene replacement or editing to correct mutations in CF; however, data regarding their safety and efficacy will likely be unavailable for several years.

Lifetime per-patient costs are approximately $306,332, the majority of which are associated with hospital costs (58%), followed by pharmacological treatments (29%), medical services (10%), complications (2%), and diagnostic testing (1%).[17] These costs are expected to rise with the anticipated introduction and availability of the novel investigational therapies discussed above.

IMPLICATIONS FOR MANAGED CARE AND CONCLUSIONS

The reasons for improved survival in CF are complex and include many factors, such as earlier diagnosis, improved control of pulmonary infection, aggressive nutritional intervention, and enhanced monitoring of patients.[18] With the advent of newer and targeted therapies, another focus of change in CF has appeared: that of cost containment in the medical profession.

Earlier this year, the Institute for Clinical and Economic Review (ICER) released an Evidence Report regarding the three available CFTR modulators: ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor.[19] In a statement, ICER's chief scientific officer, Dan Ollendorf, stated, "Our analysis suggested that discounts of up to 77% would be needed to bring the prices into alignment with their clinical value to patients."[20] While acknowledging that these therapies offer significant benefits for patients, he added that the drugs' prices "produce overall costs that are far in excess of those needed to reach commonly cited cost-effectiveness thresholds."[20]

In a response letter to ICER's Evidence Report, the manufacturer's vice president of government affairs and public policy, Samantha Ventimiglia, noted that ICER's "analyses utilized a series of arbitrary modeling choices that fail to capture the full benefits of [their] medicines, thereby intentionally leading to worse outcomes for these transformative medicines. Omission of such evidence for medicines that are the first to treat the underlying cause of CF and fundamentally change the course of disease progression for patients is particularly egregious."[21]

Following release of the ICER Evidence Report, Vertex and several patient groups, including CFF, submitted concerns about the report.[20] An ICER spokesperson communicated to FiercePharma that the report's findings were adjusted based on the public comments; however, the results from the draft report and the June 2018 Final Evidence Report and Meeting Summary revealed that the conclusions remained largely unchanged.

Angus Liu of FiercePharma says these discussions have resulted in some suggesting that the "ICER report may stifle innovation and provide justification for payors to refuse coverage."[20] In a response to the draft ICER review, CFF noted that they "believe the report does not capture important key points about modulators, including: Early initiation and long-term use of these drugs will have profound implications in altering the course of disease … CFTR modulators have clinical and quality of life benefits beyond lung function … The societal benefits associated with modulators will be seen in time."[22] A CFF spokesperson further commented, "While the cost-effectiveness analyses can be informative, they must be used carefully and as part of a holistic evaluation of the value a treatment provides. If applied to inform real-world coverage decisions, the inaccuracies and limitations of ICER's model must be recognized. We have serious reservations about the model used to generate this report and are concerned that it does not reflect the clinical significance of CFTR modulators and the realities that patients experience."[22]

While the clinical and biological understanding of CF has continued to evolve, it has become increasingly important for payors to remain

Fortunately, advances in CF have led to consistently improving survival, but with it come several managed care questions targeting improving care while streamlining costs.

up-to-date regarding the availability of investigational agents and the cost of existing and novel therapies. New diagnostics and evolving agents that target CFTR offer the potential to more effectively individualize management from the time CF is suspected to the point where treatment is started. Several types of emerging agents hold promise for the future of the CF treatment landscape. Fortunately, advances in CF have led to consistently improving survival, but with it come several managed care questions targeting improving care while streamlining costs.

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Regulatory Update

CMS Final Rule and Drug Pricing

CMS Final Rule – April 2018

In April 2018, the Centers for Medicare & Medicaid Services (CMS) issued final rule CMS-4182-F, effective June 15, 2018, finalizing policy changes and updates for Medicare Advantage (MA) and the Prescription Drug Benefit Program (Part D) for 2019.[1] The MA and Part D programs have successfully created space for innovative approaches in providing benefits to enrollees. CMS outlines several objectives that this final rule addresses in an effort to promote innovation and equip MA and Part D sponsors with new tools aiming to improve quality of care and expand plan choices for enrollees.[2]

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CHANGES TO THE STAR RATINGS PROGRAM FOR 2019 AND BEYOND

CMS announced new guidelines and modifications to achieve transparency and accuracy in the Star Ratings Program. More specifically, CMS is codifying aspects of the Part C and D Star Ratings methodology as well as setting new rules for the assignment of Star Ratings. For example, new rules will be implemented in 2019 relating to the assignment of Star Ratings when contracts consolidate to ensure an accurate reflection of the performance of all contracts involved in the consolidation.[2] Additionally, new methods have been introduced to increase Star Ratings predictability to encourage plans to invest in the improvement of care for beneficiaries.

ELIMINATES LIMIT ON MEDICARE ADVANTAGE PLAN VARIETY

This final rule addresses limits on MA organizations by eliminating the requirements that MA plans offered by the same organization in the same county comply with limits requiring differences between the plans, beginning in 2019.[2] This requirement is eliminated in an effort to address the concern that organizations may reduce the value of benefit offerings to comply with unnecessary limits. Ultimately, this elimination may lead to innovative benefit design and more flexible and inclusive consumer engagement and decision-making, with the goal of informed plan choices for beneficiaries and family members.

ALLOWS PLAN SPONSORS TO SUBSTITUTE CERTAIN GENERICS FOR BRAND-NAME DRUGS

Part D sponsors are permitted the flexibility to immediately substitute generics for brand-name drugs on the same or lower cost-sharing tier. Certain requirements must be met to receive this flexibility, including alerting beneficiaries of substitution policies and providing notice when a substitution is set to occur.

UPDATES MAXIMUM OUT-OF-POCKET AND COST-SHARING LIMITS

The final rule includes a revision to maximum out-of-pocket limits, giving

CMS the authority to modify and adjust these limits starting in 2020.[2] CMS plans to utilize this authority to incentivize and encourage plan offerings with lower maximum out-of-pocket limits.

PERMITS USE OF ELECTRONIC COMMUNICATION AND STREAMLINES MARKETING APPROVALS

CMS's final rule furthers the previously launched Patients Over Paperwork initiative, which works to reduce regulatory burdens by authorizing plans to use electronic posting to satisfy disclosure requirements, thus eliminating requirements that plans submit overlapping accounting information, and streamlining government review and approval of plans' marketing materials.[2]

The rule implemented numerous additional policy changes, which collectively seek to address previously applied unnecessary burdens and increase flexibility and efficiency throughout the MA and Part D programs. These policy changes are estimated to result in about $295 million in annual savings for the Medicare program from 2019 through 2023.[2]

American Patients First – May 2018

On May 11, 2018, the U.S. Department of Health and Human Services (HHS) released "American Patients First": The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs. Split in two parts, the 44-page blueprint includes immediate regulatory actions by HHS (Pages 23-25), which includes such changes as prohibiting Part D plan sponsors' contracts from including "gag clauses." In the section entitled, "Further Actions Under Review" (Pages 26-38), are a range of potential regulatory and legislative proposals relating to the 340B and Medicaid Drug Rebate programs, fiduciary duty for pharmacy benefit managers, moving Medicare Part B payable drugs to Part D, operating a Competitive Acquisition Program for Part B, and site neutrality for physician-administered drugs, among many others.

The plan describes four priorities, noted below, of the Trump administration and lists dozens of policy proposals, though many are concepts under consideration for which HHS is soliciting public comment.

IMPROVED COMPETITION

To improve competition, HHS may take steps to prevent gaming of regulatory processes governing prescription drug development. For example, the U.S. Food and Drug Administration (FDA) has since issued a guidance that addresses avenues manufacturers may use for shared system risk evaluation and mitigation strategies (REMS) to delay or block competition from emerging generic products. The issuance of new FDA policies may improve market availability, competitiveness, and accessibility of biosimilars.[3]

BETTER NEGOTIATION

HHS may direct CMS to develop and test innovative models encouraging value-based payment models for prescription drugs. The blueprint notes that these models should aim to hold manufacturers accountable while equipping Medicare providers, payors, and states with tools and resources to simplify the management of spending for high-cost therapies.[3]

HHS also may provide Part D plan sponsors the opportunity to adjust and restructure formulary or benefit design in the event of price increases for sole source generic drugs. This flexibility provides Part D plan sponsors the discretion to respond to price increases for sole source generic drugs.[3]

Additional potential strategies outlined in the blueprint include:[3]

1. Providing Medicare Part D plan sponsors more flexibility with respect to formulary and benefit designs (including permitting mid-year changes in formularies and managing high-cost drugs.
2. Updating the methodology for Medicare Part D plan Star Ratings to recognize plans that are appropriately managing utilization of high-cost drugs.
3. Leveraging the authority established by the Competitive Acquisition Program for Part B Drugs and Biologicals, which generally provides physicians the discretion to choose between ordering such drugs from a vendor selected via competitive bidding or direct purchase with the option of being paid under current average sales price.

LOWERED LIST PRICES

To promote transparency and consumer awareness, HHS may call on the FDA to evaluate how list prices could be included in direct-to-consumer advertising.[3] HHS may also seek to equip

On May 11, 2018, the U.S. Department of Health and Human Services (HHS) released "American Patients First": The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs.

Additionally, to ensure that patients are aware of available alternatives and pricing information, HHS may require Part D plans to provide complete information to members inclusive of all drug price increases and lower-cost alternatives as part of the summary materials sent to Medicare beneficiaries.[3]

patients, families, and caregivers with the additional information they need to make informed decisions and predict the costs they may face. To achieve this objective, CMS may be directed to make Medicare and Medicaid prices more transparent, holding drugmakers accountable for their price increases and highlighting drugs that have not seen price increases.[3]

REDUCED PATIENT OUT-OF-POCKET SPENDING

In an effort to lessen out-of-pocket spending for patients, HHS may work to prohibit pharmacy "gag clauses," or Part D contracts that prevent pharmacists from informing patients when they could achieve lower costs by not billing prescriptions through their insurance plans.[3] Additionally, to ensure that patients are aware of available alternatives and pricing information, HHS may require Part D plans to provide complete information to members inclusive of all drug price increases and lower-cost alternatives as part of the summary materials sent to Medicare beneficiaries.[3]

On May 16, HHS published a formal Request for Information (RFI) on the various questions and policy proposals discussed in the blueprint. HHS is interested in all suggestions to improve the affordability and accessibility of prescription drugs to help shape future policy development and agency action. Public comments are due by July 16.

You may submit comments to the Department of Health and Human Services electronically by visiting www.regulations.gov and following the "Submit a comment" instructions, or by mail, by writing to the Department of Health and Human Services at 200 Independence Ave., SW, Room 600E, Washington DC, 20201.

The blueprint describes four priorities: improved competition, better negotiation, lowered list prices, and reduced patient out-of-pocket spending.

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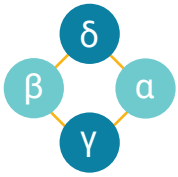

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Asthma

Increasing Competition on the Medical Benefit

Asthma is a chronic disease affecting the lungs that is characterized by the occurrence of exacerbations, commonly referred to as asthma attacks.[1,2] During an asthma attack, the airways become swollen and inflamed and the muscles surrounding the airways contract, resulting in the narrowing of the bronchial tubes. In addition, excess mucus production may occur and cause a further narrowing of the airways. During an attack, patients may experience wheezing, severe shortness of breath/difficulty breathing, chest tightness, and coughing.[1,2] It is estimated that approximately one in 12 people in the U.S. has asthma, and the incidence appears to be increasing each year.[3] Asthma does appear to be slightly more common in children than adults, with approximately one in 10 children diagnosed.[3]

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According to the Centers for Disease Control and Prevention, approximately one in two people with asthma had an asthma attack in 2008, many of which may have been preventable.[3] In addition to limiting an individual's quality of life, asthma is associated with a significant financial burden. In 2007 alone, asthma cost the U.S. healthcare system approximately $56 billion in medical costs, lost productivity, and early death.[3]

While the exact cause of asthma is difficult to determine with certainty, several potential factors may play a role.[4] Asthma appears to have a genetic link, as individuals who have a parent diagnosed with asthma are at a greater risk of developing the disease. In addition, individuals with certain allergic conditions, those who experienced inflammatory respiratory infections during infancy or early childhood, and those who had exposure to certain allergens, irritants, or viral infections in infancy or early childhood may be at greater risk for developing asthma.[4]

Treatment of Asthma

A diagnosis of asthma is based on patient history, physical examination, and laboratory findings. The disease is categorized as mild, moderate, or severe persistent, and patients who have any level of asthma may have exacerbations that are considered mild, moderate, or severe in nature.[5] According to the asthma treatment guidelines from the Global Initiative for Asthma and the National Heart, Lung, and Blood Institute's National Asthma Education and Prevention Program, there are two main goals for the treatment of asthma — reducing impairment and risk.[5,6] By reducing impairment, the goal is to decrease the frequency and intensity of symptoms, as well as the functional limitations that a patient experiences.[5,6] By reducing the risk, the goal is to prevent subsequent asthma attacks, the progressive decline of lung function, and adverse effects from medications.[5,6]

The key tenets of pharmacologic treatment include the treatment of acute episodes (i.e., asthma attacks) and the prevention of future attacks through the careful control of symptoms.[5,6] The treatment of asthma follows a stepwise approach, with medications being added or removed as the frequency and severity of the disease changes.

GOALS FOR THE SUCCESSFUL MANAGEMENT OF ASTHMA[5]

- Achieve and maintain control of symptoms
- Maintain normal activity levels, including exercise
- Sustain lung function as close to normal as possible
- Prevent asthma attacks
- Avoid adverse effects from asthma medications
- Prevent asthma-related death

It is estimated that approximately one in 12 people in the U.S. has asthma, and the incidence appears to be increasing each year.

Therapy selection depends on the degree of impairment (i.e., occurrence of symptoms, nighttime awakenings, use of a short-acting beta$_2$ agonist [SABA], interference with normal activity, and lung function) and the patient's risk (i.e., asthma exacerbations requiring oral systemic corticosteroids). For individuals with low impairment and risk, the preferred initial treatment option is a SABA, such as albuterol. From there, other classes of medications may be added on as the severity of disease increases (see Table 1).[5,6]

Biologics for the Treatment of Asthma

Although traditional treatments such as inhaled corticosteroids (ICS) and long-acting beta agonists (LABAs) have demonstrated efficacy in the treatment of mild to moderate asthma, many patients with severe disease may be unable to achieve adequate disease control with these options.[5-7] While it is estimated that only 3 to 10% of patients with asthma have severe disease, these patients account for more than 60% of the total asthma healthcare spend, which is primarily associated with the cost of medications.[7]

It is important to distinguish between severe asthma and asthma that is difficult to treat. Difficult-to-treat asthma is defined as asthma that remains uncontrolled despite high-dose ICS or other controllers, or requires such treatment to remain well-controlled.[7] Severe asthma is a subtype of difficult-to-treat asthma that includes patients whose asthma remained uncontrolled despite treatment with high-dose ICS in combination with a LABA, a leukotriene modifier, or theophylline for the previous year; those who required treatment with systemic glucocorticoids for at least half of the previous year; or those who require such treatments to remain well-controlled. Within the past 20 years, several new, targeted therapies for the treatment of severe asthma have received Food and Drug Administration (FDA) approval.[7]

Anti-IgE Therapy

Omalizumab (Xolair®, Genentech and Novartis) was the first targeted therapy to receive FDA approval in 2003 for the treatment of moderate to severe persistent asthma in patients who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS.[8] Omalizumab is a subcutaneously administered monoclonal antibody that binds to free IgE in order to prevent the activation of mast cells, basophils, and dendritic cells, and downregulates the high-affinity receptor for the Fc region of IgE. In clinical trials, when added to ICS, treatment with omalizumab was associated with a 45% reduction in the frequency of severe exacerbations and an 85% reduction in hospitalizations.[8,9] Furthermore, the addition of omalizumab allowed for lower doses of inhaled glucocorticoids and less frequent use of SABA therapy for acute symptoms. Based on the prescribing information, pretreatment serum IgE and body weight are used to determine the appropriate dose.[8,9] According to current consensus guidelines, treatment with omalizumab may be considered in patients with se-

TABLE 1. STEPWISE APPROACH FOR TREATMENT OF ASTHMA IN PATIENTS ≥12 YEARS OF AGE[5,6]

Step 1	**Preferred:** SABA (as needed) **Alternative(s):** Consider low-dose ICS
Step 2	**Preferred:** Low-dose ICS **Alternative(s):** LTRA or low-dose theophylline
Step 3	**Preferred:** Low-dose ICS + LABA **Alternative(s):** Medium or high-dose ICS or low-dose ICS + LTRA or theophylline
Step 4	**Preferred:** Medium or high-dose ICS + LABA **Alternative(s):** Medium or high-dose ICS + LABA + tiotropium or medium or high-dose ICS + LTRA or theophylline
Step 5	**Preferred:** Refer for add-on treatment (e.g., tiotropium, anti-IgE*, anti-IL5† **Alternative(s):** Consider adding low-dose oral corticosteroids

*Such as omalizumab
†Such as mepolizumab, benralizumab, or reslizumab
Abbreviations: ICS=inhaled corticosteroid, IgE = immunoglobulin E, IL=interleukin, LABA=long-acting beta$_2$ agonist, LTRA=leukotriene receptor antagonist

TABLE 2. ORAL AND INHALED MEDICATIONS FOR THE TREATMENT OF ASTHMA[6]	
SHORT-ACTING, AS-NEEDED RESCUE MEDICATIONS	
SABAs	
Brand Name	**Generic Name**
ProAir®, Proventil®, Ventolin®	Albuterol
Xopenex®, Xopenex® HFA	Levalbuterol
LONG-TERM CONTROLLER MEDICATIONS	
ICS	
Brand Name	**Generic Name**
Aerospan HFA®	Flunisolide
Alvesco®	Ciclesonide
Arnuity Ellipta®	Fluticasone furoate
Asmanex® HFA, Asmanex Twisthaler®	Mometasone furoate
ArmonAir RespiClick®	Fluticasone propionate
Flovent Diskus®, Flovent HFA®	Fluticasone propionate
Pulmicort® Flexhaler™, Pulmicort Respules®	Budesonide
Qvar® RediHaler™	Beclomethasone dipropionate
LABAs	
Arcapta Neohaler®	Indacaterol
Brovana®	Arformoterol
Foradil®	Formoterol, inhaler
Perforomist®	Formoterol fumarate, solution for nebulizer
Serevent Diskus®	Salmeterol
Striverdi®	Olodaterol
ICS/LABA COMBINATION PRODUCTS	
Advair Diskus®	Fluticasone and salmeterol
AirDuo RespiClick®	Fluticasone and salmeterol
Breo Ellipta®	Fluticasone and vilanterol
Dulera®	Formoterol and mometasone
Symbicort®	Budesonide and formoterol
LEUKOTRIENE MODIFIERS/ANTAGONISTS	
Accolate®	Zafirlukast
Singulair®	Montelukast
Zyflo®, Zyflo CR®	Zileuton

vere persistent asthma who are not adequately controlled on high-dose ICS and LABAs if there is evidence of sensitivity to a perennial allergen and the serum IgE level is within the appropriate range.[6]

Anti-IL5 Therapies

Anti-IL5 therapies differ from the currently available anti-IgE product in that omalizumab is indicated for the treatment of severe allergic asthma, while anti-IL5 therapies are indicated for the treatment of severe eosinophilic asthma.[7,8] IL5 plays a key role in promoting eosinophilic inflammation. The first two anti-IL5 therapies to receive FDA approval, mepolizumab (Nucala®, GlaxoSmithKline) and reslizumab (Cinqair®, Teva), work by binding directly to IL5 to prevent binding with the IL5 receptor, thus preventing the activation of the eosinophilic inflammation cascade.[7,10,11] The third agent, benralizumab (Fasenra®, AstraZeneca) works slightly differently in that it targets the IL5 receptor directly to produce eosinophil apoptosis.[7,12]

Given that it was the first anti-IL5 therapy to come to market in 2015, the majority of the efficacy data available for agents within this class are for mepolizumab.[7,10] In clinical trials, treatment with mepolizumab has been shown to reduce asthma exacerbations by 40 to 60% in patients who experienced at least two exacerbations in the past year and a peripheral blood eosinophil count of ≥ 300 cells/μL.[7,10] In addition, treatment with mepolizumab has been associated with a mean reduction of 50% in oral glucocorticoid dose compared to treatment with placebo. The efficacy of mepolizumab appears to be greater in patients with more severe disease based on the number of asthma exacerbations in the previous year and a serum eosinophil count at baseline.[7,10] Although no head-to-head studies have been conducted comparing anti-IL5 therapies, they appear to have similar efficacy in terms of reducing asthma exacerbations; however, it is important to note that each agent has demonstrated clinical efficacy in patients with slightly different peripheral blood eosinophil counts.[7,10-13] Mepolizumab has demonstrated efficacy in

patients with peripheral blood eosinophil counts ≥150 cells/μL, benralizumab has efficacy in patients with counts ≥300 cells/μL, and reslizumab has efficacy in patients with counts ≥400 cells/μL.[7,10-13] While all three agents may be effective in patients with higher peripheral eosinophil counts, mepolizumab may be more effective in patients with lower counts.

Anti-IL5 therapies also differ slightly in how they are administered. Because they are biologic agents and are associated with the potential for hypersensitivity reactions, all three agents must be administered by a healthcare professional and monitored accordingly.[10-12] Mepolizumab and reslizumab are both administered every four weeks; however, mepolizumab is given subcutaneously as three separate injections, while reslizumab is infused intravenously over 20 to 50 minutes. Benralizumab has an advantage over the other two agents in that it can be administered subcutaneously every eight weeks after the first three doses (which are given every four weeks). The less-frequent dosing may be an appealing option for patients who have difficulty adhering to their treatment regimen. Lastly, it is important to note that mepolizumab and benralizumab are FDA-approved for use in individuals 12 years of age and older, while reslizumab is only approved for use in adults.[10-12] Details regarding these treatments are listed in Table 3.

Biologics Pipeline

IL4 and IL13 have been found to play a key role in the pathogenesis of atopic asthma.[13] These two cytokines are expressed by Th2 cells and mast cells, and they share a common target receptor, the IL4 receptor α.[13] Binding of IL4 or IL13 to the IL4 receptor activates a downstream cascade that results in airway inflammation, airway remodeling, mucus secretion, and activation of smooth muscle cells of the airway, ultimately leading to airway hyperresponsiveness. Given the central role these cytokines play, there has been extensive development within the pharmaceutical pipeline of biologics designed to target the IL4/IL13 pathway.[13]

While it is estimated that only 3 to 10% of patients with asthma have severe disease, these patients account for more than 60% of the total asthma healthcare spend, which is primarily associated with the cost of medications.

Dupilumab

Dupilumab (Dupixent®, Regeneron Pharmaceuticals), a monoclonal antibody targeting the IL4 receptor subunit, was FDA-approved in 2017 for the treatment of atopic dermatitis.[14] Dupilumab is currently under review by the FDA for the treatment of patients 12 years of age and older with moderate-to-severe asthma, with an FDA decision expected by October 20, 2018.[15]

The supplemental biologics license application for dupilumab included data from three pivotal trials in the LIBERTY ASTHMA clinical program.[16] In the phase III LIBERTY ASTHMA QUEST trial (N=1,902), treatment with 300 mg of dupilumab as an add-on to standard therapies reduced asthma exacerbations by 46% compared to placebo at week 52 (P<0.001).[16] In the phase III LIBERTY ASTHMA VENTURE trial (N=210), patients with severe asthma and regular use of maintenance oral corticosteroids were enrolled, and the median baseline eosinophil count was 260 cells/μL.[17] In the overall study population, 80% of patients treated with dupilumab reduced their oral corticosteroid dose by at least half, while maintaining asthma control, compared to 50% of patients who received placebo.[17] In patients with a baseline eosinophil count of ≥ 300 cells/μL, 88% reduced their oral corticosteroid dose by at least half, compared to 52% in the placebo treatment category.[17] Patients treated with dupilumab also experienced 59% fewer asthma exacerbations compared to those treated by placebo in the overall population, and patients with eosinophil counts of ≥ 300 cells/μL experienced 71% fewer attacks.[17]

Although no head-to-head studies have been completed comparing dupilumab to the available biologic therapies for asthma, clinical data thus far suggests that treatment with dupilumab is at least as effective in reducing asthma exacerbations.[16,17] In addition, dupilumab is administered subcutaneously every two weeks and may be self-administered by the patient after appropriate training by a healthcare provider.[14]

Several other agents within this emerging class are in development for asthma, including lebrikizumab and tralokinumab, which both target IL13; however, data thus far has been mixed.[13]

Tezepelumab

Tezepelumab is a potential first-in-class monoclonal antibody that targets epithelial cell-derived cytokine thymic stromal lymphopoietin (TSLP).[18] TSLP is an upstream driver of inflammation in

TABLE 3. EXISTING BIOLOGICS

Drug Name	Pharmacology	Manufacturer
Cinqair (IV Q4W)	IL5 antagonist	Teva
Fasenra (SC Q4W then Q8W)	IL5 antagonist	AstraZeneca
Nucala (SC Q4W)	IL5 antagonist	GlaxoSmithKline
Xolair (SC Q4W)	Anti-IgE	Genentech, Novartis

Abbreviations: IL5=interleukin-5, IgE=immune globulin E, IV=intravenous, Q4W=every four weeks, Q8W=every eight weeks, SC=subcutaneous

asthma that is produced in response to environmental and pro-inflammatory stimuli, and TSLP expression is higher in the airways of patients with asthma. Tezepelumab works by binding to TSLP and preventing its interaction with the TSLP receptor complex.[18] As such, tezepelumab is currently being studied for the treatment of patients with severe uncontrolled asthma. In the phase IIb PATHWAY trial (N=584), treatment with subcutaneous tezepelumab every four weeks, in combination with standard of care, resulted in reductions in asthma exacerbations rates of 61 to 71% compared to placebo (P<0.001). Furthermore, results were similar regardless of baseline blood eosinophil count.[18]

Because tezepelumab targets TSLP, treatment may effectively block the IL4, IL5, and IL13 pathways and produce more broad physiological effects than targeting individual cytokines, as the currently available biologics do.[18] In addition, tezepelumab has demonstrated efficacy in clinical trials regardless of eosinophil count, which may make it an important treatment option in patients with non-eosinophilic asthma.[18,19] A regulatory filing for tezepelumab in severe, uncontrolled asthma is planned for 2021.[20]

Implications for Managed Care

Over the past few years, payors have seen oral and inhaled therapies' overall trends in prescription spending begin to decrease through the pharmacy benefit. These decreases are mainly driven by increased competition and rebate strategies. While the trends have been decreasing through the pharmacy benefit, Magellan Rx Management has seen the trends begin to increase through the medical benefit. The 2017 Magellan Rx Management Medical Pharmacy Trend Report shows that the asthma/COPD drug category PMPM spend increased 28% from $0.28 in 2015 to $0.36 in 2016.[21]

With biologics on the market and new biologics in the pipeline, the treatment of asthma is becoming increasingly targeted and patient-specific. It is crucial for clinicians and payors to have a solid understanding of how each biologic works, as well as the advantages and disadvantages associated with each agent, in order to select the most appropriate therapies for their patients.

The 2017 Magellan Rx Management Medical Pharmacy Trend Report shows that the asthma/COPD drug category PMPM spend increased 28% from $0.28 in 2015 to $0.36 in 2016.

In addition to novel mechanisms of action, biologic agents in development also bring additional market competition. With several agents targeting IL5 currently on the market, payors may consider selecting a preferred product for additional cost savings. Payors will also need to consider exploring value-based contracts on these medications to ensure the use of medication is leading to an offset in hospitalization/emergency room utilization and other medical costs associated with poor asthma control.

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Human Immunodeficiency Virus

Evolving Treatment Landscape

Recent estimates suggest that there are approximately 1.1 million Americans living with human immunodeficiency virus (HIV), with 39,782 new infections diagnosed in 2016.[1,2] Furthermore, it is estimated that approximately one in seven individuals who have HIV is unaware of their disease.[2] If left untreated, HIV progresses to acquired immunodeficiency syndrome (AIDS), the most severe stage of HIV that results in patients becoming severely immunocompromised and at risk for developing opportunistic infections. In individuals who progress to AIDS and continue to be untreated, the average survival is approximately three years.[3] If these patients contract an opportunistic infection, the average life expectancy drops to approximately one year.[3] In 2014, there were more than 12,000 AIDS-related deaths in the U.S. alone.[2]

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Vice President of Pharmacy
Amida Care

Fortunately, the majority of individuals living with HIV in the U.S. do not progress to AIDS due to the availability of effective antiretroviral therapy (ART) that halts disease progression; however, there is much progress to be made, as ART coverage was estimated to be just 37% in 2011.[1] While the rates of annual HIV infections and related deaths in the U.S. are decreasing, there continues to be a high rate of new cases among certain groups, including certain ages and ethnicities of men who have sex with men (MSM), and those in Southern states, which accounted for 50% of new infections in 2014.[4] Within the South specifically, access to insurance is a concern, as there are disparities in healthcare for people of color in this geographic region.[4] More than four in ten of all people of color reside in the South, with nearly six in ten of Black Americans residing in this area.[4] Of note, those living in the South are more likely to be poor compared to those living in other areas of the country, and are also more likely to be uninsured than those living in other parts of the country.[4] Unfortunately, Medicaid and Children's Health Insurance Program (CHIP) eligibility levels are more limited in this region as well, and there are areas of the South where Medicaid coverage expansion has not taken place, resulting in health disparities among this patient group.[4] Early diagnosis of HIV coupled with early treatment initiation is imperative, as it may allow individuals to have a life span that is similar to that of an individual without HIV.[5]

Given the high efficacy associated with currently available ART in combatting the progression of HIV to AIDS, linkage to care, retention in care, and adherence to ART — collectively referred to as the HIV treatment cascade — are of the utmost importance in achieving optimal patient outcomes.[5] According to the National Institutes of Health (NIH), following a diagnosis of HIV, 75% of individuals are linked to care within 30 days; however, only about 57% of those individuals are retained in care, and poor retention in care is associated with a greater risk of death.[5] Poor retention in care is more

TABLE 1. THE HIV TREATMENT LANDSCAPE[6]		
Drug Class/Generic Name	**Brand Name**	**Generic Availability (Y/N)**
NRTIs		
Abacavir	Ziagen®	Y
Didanosine	Videx®, Videx® EC	Y
Emtricitabine	Emtriva®	N
Lamivudine	Epivir®	Y
Stavudine	Zerit®	Y
Tenofovir disoproxil fumarate	Viread®	Y
Zidovudine	Retrovir®	Y
NNRTIS		
Efavirenz	Sustiva®	Y
Etravirine	Intelence®	N
Nevirapine	Viramune®, Viramune® XR	Y
Rilpivirine	Edurant®	N
PIs		
Atazanavir	Reyataz®	Y
Darunavir	Prezista®	N
Fosamprenavir	Lexiva®	Y
Indinavir	Crixivan®	N
Nelfinavir	Viracept®	N
Saquinavir	Invirase®	N
Tipranavir	Aptivus®	N
Fusion inhibitor		
Enfuvirtide	Fuzeon®	N
Entry inhibitor/CCR5 antagonist		
Maraviroc	Selzentry®	N
INSTIs		
Dolutegravir	Tivicay®	N
Elvitegravir	Vitekta®	N
Raltegravir	Isentress®	N
PK boosters		
Cobicistat	Tybost®	N
Ritonavir**	Norvir®	Y
Post-attachment inhibitor		
Ibalizumab	Trogarzo®	N
Combination medications		
Abacavir/lamivudine	Epzicom®	Y
Abacavir/dolutegravir/lamivudine	Triumeq®	N
Abacavir/lamivudine/zidovudine	Trizivir®	Y
Atazanavir/cobicistat	Evotaz®	N
Bictegravir/emtricitabine/tenofovir alafenamide	Biktarvy®	N
Darunavir/cobicistat	Prezcobix®	N
Dolutegravir/rilpivirine	Juluca®	N
Efavirenz/emtricitabine/tenofovir disoproxil fumarate	Atripla®	N
Efavirenz/lamivudine/tenofovir disoproxil fumarate	Symfi™, Symfi Lo™	N
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate	Genvoya®	N
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	Stribild®	N
Emtricitabine/rilpivirine/tenofovir alafenamide fumarate	Odefsey®	N
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate	Complera®	N
Emtricitabine/tenofovir alafenamide fumarate	Descovy®	N
Emtricitabine/tenofovir disoproxil fumarate	Truvada®	N
Lamivudine/tenofovir disoproxil fumarate	Cimduo®	N
Lamivudine/zidovudine	Combivir®	Y
Lopinavir/ritonavir	Kaletra®	N***

Abbreviations: CCR5=C-C chemokine receptor type 5, INSTIs=integrase strand transfer inhibitors, NRTIs=nucleoside reverse transcriptase inhibitors, PIs=protease inhibitors, PK=pharmacokinetic

**Also considered a PI; however, ritonavir is primarily used as a PK booster for PIs ***Generic available for lopinavir/ritonavir 80-20 mg/mL solution, only

Initial Characteristics for Consideration in All Individuals with HIV[5]

- Pretreatment viral load
- Pretreatment CD4 count
- HIV genotypic drug resistance testing
- HLA-B*5701 status
- Individual preferences, values
- Expected medication adherence to regimen

Regimen-Specific Characteristics for Consideration

- Genetic barrier to resistance for regimen
- Potential adverse effects
- Known or potential interactions with other medications
- Pill burden
- Dosing frequency
- Availability of fixed-dose combination products
- Requirement for administration with food
- Cost

commonly observed in patients with substance use disorder, mental health disorder(s), poor socioeconomic status, and a lack of health insurance. It is also commonly observed among those with schedules that make medication adherence difficult, those who have a history of incarceration, and patients who face stigma due to their HIV status.[5] The factors influencing retention in care may also affect adherence to ART. Social determinants of health, including, but not limited to, food security, adequate or stable housing, and access to insurance, all have a significant impact on adherence to treatment goals, medications, and ultimately, outcomes.[5] In addition, characteristics of the ART regimen can greatly influence the patient's adherence. For example, once-daily regimens with a low pill burden, no food coadministration requirements, and a favorable safety profile are associated with greater adherence.[5]

Current Treatment Landscape

There are currently 25 antiretroviral drugs across seven mechanistic classes that are FDA-approved for the treatment of HIV infection (see Table 1).[6] These classes include the nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor, a CCR5 antagonist, integrase strand transfer inhibitors (INSTIs), and, more recently, a post-attachment inhibitor, ibalizumab (Trogarzo®).

Ibalizumab was approved by the FDA in March 2018 for the treatment of HIV-1 in heavily treatment-experienced adults with multidrug resistant HIV-1 who were failing their current ART regimen.[6,7] The FDA approval of ibalizumab represented the first novel mechanism of action for the treatment of HIV in more than a decade. Ibalizumab is a monoclonal antibody that blocks HIV from infecting host cells by binding to extracellular domain 2 of the CD4+ receptor, a site that is different from what is targeted by other ARTs currently on the market.

The FDA approval of ibalizumab was based on evidence from a single clinical trial (N=40) of adult patients with HIV-1 infection who were no longer responding to various anti-HIV treatments.[7] The trial consisted of three periods:[7]

1. an observation period (day 0 to day 6) during which patients continued their old therapy
2. a therapy period (day 7 to day 13) during which patients continued their old therapy and received ibalizumab
3. a maintenance period (day 14 to week 25) during which patients received a lower dose of ibalizumab in addition to other anti-HIV drugs

The study's primary endpoint was the percentage of patients achieving at least a 0.5 log10 (or 70%) viral load reduction from baseline seven days after receiving a 2,000 mg loading dose of ibalizumab and no adjustment to the failing background regimen.[7] The results of the trial demonstrated that treatment with ibalizumab, when combined with an optimized background regimen that included at least one other active ART for up to 24 weeks of treatment, reduced viral load within seven days after the first dose of functional monotherapy, and maintained the treatment response.[7] More than 80% of patients achieved the study's primary endpoint.[7] After 24 weeks of treatment, the average viral load reduction was 1.6 log10, with 43% of patients achieving undetectable viral loads.[6] Ibalizumab is administered intravenously once every two weeks and must be given in combination with other ARTs.[7] The wholesale acquisition cost of ibalizumab is $9,080 for four weeks of therapy.

In addition to these seven classes of ART, ritonavir and cobicistat are used as pharmacokinetic (PK) boosters to improve the PK profiles of certain ARTs, including PIs and elvitegravir.[6]

The initial treatment approach generally consists of two NRTIs in combination with an INSTI, an NNRTI, or a PK-enhanced PI (see Table 2). The goal of treatment is to select a potent, safe, tolerable regimen that is easy for the patient to adhere to in order to achieve

TABLE 2. RECOMMENDED REGIMENS FOR ART-NAÏVE PATIENTS[5]
INSTI + 2 NRTIs
dolutegravir/abacavir/lamivudine (Triumeq®) (only for patients who are HLA-B*5701 negative) (AI)
dolutegravir (Tivicay®) plus either tenofovir disoproxil fumarate/emtricitabine (Truvada®) (AI) or tenofovir alafenamide fumarate/emtricitabine (Descovy®) (AI)
elvitegravir/cobicistat/tenofovir alafenamide fumarate/emtricitabine (Genvoya®) (AI) or elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine (Stribild®) (AI)
raltegravir (Isentress®) plus either tenofovir disoproxil fumarate/emtricitabine (Truvada®) (AI) or tenofovir alafenamide fumarate/emtricitabine (Descovy®) (AII)

Rating of recommendations: A=Strong

Rating of Evidence: I=Data from randomized controlled trials; II=Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies

sustained virologic control.[5] Given the complexity of the disease, the comorbidities that patients may have (e.g., hepatitis B virus, hepatitis C virus, cardiovascular disease, hyperlipidemia, etc.), other medications they may be using, and number of treatment options available, treatment selection is very patient-specific.[5]

Additionally, resistance testing should be used to guide care decisions. If a patient has achieved and maintained virologic suppression on a specific regimen, switching should be avoided to minimize disruption to the regimen.

HIV Pharmaceutical Pipeline

As it has become well-established that patient adherence to ART produces optimal clinical outcomes, there has been a great deal of focus on the development of consolidated regimens that require less frequent dosing and have improved safety profiles. In November 2017, the FDA approved the first two-drug regimen, dolutegravir/rilpivirine (Juluca®), for patients with HIV-1 who are virally suppressed and have been on their current regimen for at least six months.[8] According to a press release from the Center for Drug Evaluation and Research, limiting the number of drugs included in an HIV treatment regimen may help reduce toxicity by reducing adverse events and potential drug interactions.[8]

Cabotegravir and Rilpivirine

Rilpivirine (Edurant®) and the investigational agent cabotegravir are two long-acting injectable drugs being studied for the combination treatment of patients with HIV-1 who have achieved viral suppression.[9] Rilpivirine (Edurant®), which was FDA-approved in 2011, is an NNRTI indicated in combination with other ARTs for the treatment of HIV-1 in ART-naïve patients with HIV-1 ribonucleic acid ≤100,000 copies/mL at treatment initiation.[6] Cabotegravir is an investigational, intramuscularly administered INSTI currently being studied for its role in the treatment and prevention of HIV. The ongoing phase III Antiretroviral Therapy as Long Acting Suppression Every 2 Months (ATLAS-2M) study will enroll approximately 1,020 patients and is designed to demonstrate the non-inferiority of cabotegravir and rilpivirine administered every eight weeks compared to every four weeks over a 48-week treatment period.[9] ATLAS-2M will include patients from the ongoing ATLAS trial, in which patients were randomized to receive current ART standard of care or cabotegravir and rilpivirine every four weeks.[9]

In the previously published phase IIb LATTE-2 trial, 90% of patients treated with cabotegravir and rilpivirine intramuscularly every four or eight weeks successfully maintained viral suppression at 32 weeks, meeting the primary endpoint of non-inferiority compared to the oral comparator group (cabotegravir plus abacavir/lamivudine administered once daily).[10] Although market entry of combination treatment with cabotegravir and rilpivirine is likely more than a year away, FDA approval of an effective maintenance therapy that can be administered every four to eight weeks may represent an important treatment option for patients who are stabilized on an ART regimen but desire or require a regimen with a more flexible administration schedule.[9,10]

Key factors for those in managed care to consider include whether the injectable will fall under the pharmacy benefit, medical benefit, or both; site of administration (e.g., physician office, pharmacy, etc.); and potential cost of treatment.

PRO 140

PRO 140 is an investigational fully humanized IgG4 monoclonal antibody that belongs to a new class of ARTs, referred to as viral entry inhibitors.[11] PRO 140 is given once weekly via subcutaneous injection and works by blocking the predominant HIV (R5) subtype entry into T cells by blocking the required coreceptor, CCR5. PRO 140 does not appear to affect the normal function of CCR5 in mediating immune responses, as PRO 140 only blocks the site on CCR5 that HIV needs to enter the cell.[11] In addition, preliminary studies suggest that PRO 140 does not induce

the development of resistant viruses.[11]

PRO 140 is currently being studied in combination with highly active ART (HAART) and as a monotherapy in patients previously treated with HAART who are transitioning to a maintenance therapy.[11] In the phase IIb/III CD02 trial, heavily treatment-experienced patients with HIV who were failing their current HAART regimen were treated with PRO 140 in combination with HAART. The primary endpoint of a threefold decrease in viral load at one week was achieved (P<0.01).[11] If approved, PRO 140 may offer an important treatment option for patients who struggle with daily ART adherence, and for those who have difficulty achieving viral suppression on their current HAART.[11] An initial regulatory submission is planned for 2018 for combination therapy with HAART, with an anticipated decision in 2019.[11]

Doravirine

Doravirine is an investigational NNRTI that is currently under review by the FDA for the treatment of HIV-1.[12] Specifically, the new drug applications (NDAs) that were submitted included data for doravirine as a single, once-daily, fixed dose tablet for use in combination with other ARTs, and for use of doravirine with lamivudine and tenofovir disoproxil fumarate as a complete HIV regimen.[12] The NDAs were based on the results of two ongoing phase III trials, including DRIVE-FORWARD and DRIVE-AHEAD, which evaluated the safety and efficacy of doravirine and the fixed-dose combination regimen of doravirine/lamivudine/tenofovir disoproxil fumarate, respectively.[12] Both studies met their primary endpoints, demonstrating non-inferiority to ritonavir-boosted darunavir and to efavirenz/tenofovir disoproxil fumarate/emtricitabine, respectively.[13,14]

The FDA approval of doravirine may offer an additional treatment option with demonstrated efficacy in treatment-naïve patients. An FDA decision regarding the two NDAs is expected by October 23, 2018.[12] Of note, the fixed-dose combination tablet includes tenofovir disoproxil fumarate, a form of tenofovir that has been associated with potential safety concerns.[15] ARTs formulated with tenofovir disoproxil fumarate have warnings in their prescribing information for new onset or worsening renal impairment. As a result, creatinine clearance should be assessed prior to initiating therapy with tenofovir disoproxil fumarate for all patients, and this agent is not recommended for concurrent use or use in patients with recent use of nephrotoxic drugs.[15] In addition, treatment with tenofovir disoproxil fumarate may reduce bone mineral density.[15] Assessment of bone mineral density should be considered for all patients with a history of pathologic bone fracture or other risk factors.[15] A new formulation of tenofovir alafenamide fumarate, a prodrug of tenofovir, was approved by the FDA in November 2016.[16] Treatment with tenofovir alafenamide fumarate may be associated with a lower risk of the safety concerns, and it has been studied and approved in several combination regimens with other ARTs.[15]

Fostemsavir

Fostemsavir is an investigational prodrug of the active compound, temsavir, which is a first-in-class attachment inhibitor being studied for use with heavily treatment-experienced patients. The active metabolite, temsavir, inhibits the binding of HIV to host white blood cells by blocking the HIV gp120 receptor.[17,18]

The safety and efficacy of fostemsavir were evaluated in the phase III BRIGHTE study (N=371) that included heavily treatment-experienced patients with HIV.[17] Patients enrolled in the study had resistance, intolerability, and/or contraindications to all ARTs in at least four of the six available ART classes (prior to approval of the seventh ART class in 2018).[17] After one week of treatment, all patients receiving fostemsavir added to a failing ART regimen experienced a greater reduction in their HIV viral loads compared to patients receiving placebo (P<0.0001). After one week of treatment, all patients transitioned to fostemsavir in combination with an optimized background regimen. Of these patients, 54% achieved virologic suppression at 24 weeks.[17] Given its novel mechanism of action, fostemsavir is associated with a high genetic barrier to resistance which, coupled with its novel mechanism of action, may provide an alternative treatment option for patients with highly resistant strains of HIV who have failed other ART regimens. An NDA submission is anticipated in 2019 or 2020.[17,18]

Combination Regimens

There is continued development of fixed-dose, single-tablet combination regimens within the HIV pipeline.[19] Notably, a once-daily combination regimen including darunavir/emtricitabine/tenofovir alafenamide fumarate/cobicistat is currently under review by the FDA, with an NDA filed in September 2017.[20] In addition, a once-daily combination regimen including dolutegravir/lamivudine is currently in phase III development.[21]

Future Implications

As mentioned previously, there continues to be significant focus on the development of consolidated combination products to help improve medication adherence among patients with HIV, with the goal of ultimately improving patient outcomes.[19] In addition, the number of generic treatments available continues to increase. When patients have achieved viral suppression on a regimen that includes a generic, including multi-tablet regimens, refraining from treatment switching is recommended, even when a single-tablet regimen is available. Furthermore, newer therapies in development may offer effective treatment options in patients who are resistant to and/or have failed other ARTs. Using resistance testing to guide care is encouraged. Additionally, linking patients to care and ensuring that they are both receiving and adhering to optimized ART is crucial in ensuring that viral suppression is achieved and that patients do not progress to AIDS.[5,6,19]

In addition to combination prod-

ucts, the HIV pharmaceutical pipeline is also focusing on the development of long-acting maintenance therapies that may require less frequent dosing, thereby reducing daily medication burden.[19] Although the cost of these newer therapies will likely be higher compared to traditional ARTs (several of which are now available generically), payors should consider focusing on supporting patients in the HIV treatment cascade by promoting prevention, early diagnosis, linkage to and retention in care, and medication adherence to an optimized ART.[5,6] These areas of focus may be associated with significant opportunities for cost-savings as well as improved clinical outcomes for patients affected by HIV.

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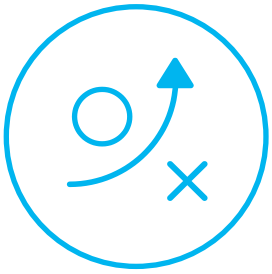

Complex population management

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We're excited to announce that two of Magellan Rx's recent publications have won prestigious Communicator Awards of Distinction! The Summer 2017 Magellan Rx Report won for "Design Features: Cover Design for Corporate Communications" and the 2017 Medicaid Pharmacy Trend Report won for "Annual Report: General-Medical for Corporate Communications."

Mostafa Kamal

Sam Srivastava

INDUSTRY EXPERTS SPEAK AT 12 INDUSTRY EVENTS

Magellan Rx experts were featured speakers at 12 industry events since January, including CEO Mostafa Kamal who spoke at the inaugural HLTH: The Future of Healthcare Conference in May on a panel "Pushing the Boundaries in Rx Solutions." Sam Srivastava, chief executive officer of Magellan Healthcare, participated in a panel discussion, "Medicaid Innovation for Populations with Complex Needs."

PIPELINE DRUG LIST

Name	Manufacturer	Clinical Use	Dosage Form	Current Phase	Approval Status	Expected FDA Approval
elagolix	AbbVie Inc.	Endometriosis	Oral	NDA	Priority review	8/6/18
patisiran	Alnylam Pharmaceuticals Inc.	hATTR (familial amyloid polyneuropathy)	IV	NDA	Breakthrough therapy; fast track; orphan drug; priority review	8/11/18
migalastat hydrochloride (Galafold™)	Amicus Therapeutics Inc.	Fabry disease	Oral	NDA	Fast track; orphan drug; priority review	8/13/18
nivolumab (Opdivo®)	Bristol-Myers Squibb Company	SCLC	IV	sBLA	Priority review	8/16/18
ivosidenib	Agios Pharmaceuticals Inc.	Relapsed/refractory IDH1-mutant AML	Oral	NDA	Fast track; orphan drug; priority review	8/21/18
alirocumab (Praluent®)	Regeneron Pharmaceuticals Inc.	Hypercholesterolemia (with apheresis)	SC	sBLA	Submitted	8/24/18
lanadelumab	Shire PLC	HAE (prophylaxis)	SC	BLA	Breakthrough therapy; fast track; orphan drug; priority review	8/26/18
lusutrombopag	Shionogi & Co. Ltd.	Thrombocytopenia	Oral	NDA	Fast track; priority review	8/26/18
eravacycline	Tetraphase Pharmaceuticals Inc.	Intra-abdominal infections (antibacterial)	IV, oral	NDA	Fast track; priority review	8/28/18
volanesorsen	Akcea Therapeutics Inc.	Familial chylomicronemia syndrome	SC	NDA	Orphan drug	8/30/18
damoctocog alfa pegol	Bayer AG	Hemophilia A	IV	BLA	Submitted	8/31/18
dasotraline	Sumitomo Dainippon Pharma Co. Ltd.	ADHD	Oral	NDA	Submitted	8/31/18
mepolizumab (Nucala®)	GlaxoSmithKline PLC	COPD (eosinophilic phenotype, maintenance)	IV, SC	sBLA	Submitted	9/7/18
C1-esterase inhibitor, recombinant (Ruconest®)	Pharming Group NV	HAE (routine prophylaxis)	IV	sNDA	Fast track; orphan drug	9/21/18
daratumumab (Darzalex®)	Janssen	Multiple myeloma (newly diagnosed)	IV	sBLA	Orphan drug	9/21/18
darunavir/emtricitabine/ tenofovir alafenamide/ cobicistat (Symtuza™)	Janssen	HIV-1 infection	Oral	NDA	Submitted	9/21/18
galcanezumab	Eli Lilly and Company	Migraine prevention	SC	BLA	Fast track	9/27/18
amisulpride (Baremsis®)	Acacia Pharma Group Ltd.	Emesis	IV	NDA	Submitted	10/5/18
duvelisib	Verastem Inc.	CLL/SLL; follicular lymphoma	Oral	NDA	Fast track; orphan drug; priority review	10/5/18
levodopa (Inbrija™)	Acorda Therapeutics Inc.	Parkinson's disease	Inhaled	505(b)(2) NDA	Submitted	10/5/18

PIPELINE DRUG LIST

Name	Manufacturer	Clinical Use	Dosage Form	Current Phase	Approval Status	Expected FDA Approval
rivaroxaban (Xarelto®)	Janssen	CAD; PAD	Oral	NDA	Fast track	10/11/18
dupilumab (Dupixent®)	Regeneron Pharmaceuticals Inc.	Asthma (severe, uncontrolled)	SC	sBLA	Submitted	10/20/18
doravirine	Merck & Co. Inc.	HIV-1 infection	Oral	NDA	Submitted	10/23/18
doravirine/lamivudine/ tenofovir disoproxil fumarate	Merck & Co. Inc.	HIV-1 infection	Oral	NDA	Submitted	10/23/18
cemiplimab	Regeneron Pharmaceuticals Inc.	CSCC	IV	BLA	Breakthrough therapy; priority review	10/26/18
revefenacin	Theravance Biopharma Inc.	COPD	Inhaled	NDA	Submitted	11/13/18
larotrectinib	Loxo Oncology Inc.	Solid tumors (NTRK gene fusion)	Oral	NDA	Breakthrough therapy; orphan drug; rare pediatric disease product	11/26/18
amifampridine phosphate (Firdapse®)	Catalyst Pharmaceuticals Inc.	LEMS	Oral	NDA	Breakthrough therapy; orphan drug	11/29/18
lorlatinib	Pfizer Inc.	NSCLC	Oral	NDA	Breakthrough therapy; orphan drug; priority review	8/1/2018 - 8/29/2018
ulipristal acetate	Allergan PLC	Uterine fibroids	Oral	505(b)(2) NDA	Submitted	8/1/2018 - 8/31/2018
canakinumab (Ilaris®)	Novartis AG	Atherosclerosis (secondary prevention)	SC	sBLA	Submitted	8/1/2018 - 10/31/2018
dacomitinib	Pfizer Inc.	Non-small cell lung cancer (first-line, locally advanced, EGFR+)	Oral	NDA	Orphan drug; priority review	9/1/2018 - 9/30/2018
moxetumomab pasudotox	AstraZeneca PLC	Hairy cell leukemia	IV	BLA	Priority review	9/1/2018 - 10/31/2018
fluticasone furoate/ umeclidinium bromide/ vilanterol (Trelegy Ellipta)	GlaxoSmithKline PLC	Asthma	Inhalation	sNDA	Submitted	Q4, 2018

Abbreviations: ADHD = attention deficit hyperactivity disorder, AML = acute myelogenous leukemia, BLA = biologics license application, CAD = coronary artery disease, CLL = chronic lymphocytic leukemia, COPD = chronic obstructive pulmonary disease, CSCC = cutaneous squamous cell carcinoma, EGFR = epidermal growth factor receptor, HAE = hereditary angioedema, hATTR = transthyretin-related hereditary amyloidosis, HIV = human immunodeficiency virus, IDH1 = isocitrate dehydrogenase 1, IV = intravenous, LEMS = Lambert-Eaton myasthenic syndrome, NDA = new drug application, NSCLC = non-small cell lung cancer, NTRK = neurotropic tropomyosin receptor kinase, PAD = peripheral artery disease, Q4 = fourth quarter, sBLA = supplemental biologics license application, SC = subcutaneous, SCLC = small cell lung cancer, SLL = small lymphocytic lymphoma, sNDA = supplemental new drug application

MAVYRET™ (glecaprevir and pibrentasvir) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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 coinfected 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 coinfected 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 coinfected 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 OATP1B1/3 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 (*hypericum perforatum*)	↓ 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, felodipine, 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

background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Glecaprevir

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.

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.

Pibrentasvir

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.

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.

Lactation

Risk Summary

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 *[see Data]*.

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.

Data

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.

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.

Pediatric Use

Safety and effectiveness of MAVYRET in children less than 18 years of age have not been established.

Geriatric Use

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.

Renal Impairment

No dosage adjustment of MAVYRET is required in patients with mild, moderate or severe renal impairment, including those on dialysis.

Hepatic Impairment

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 *[see Contraindications]*.

OVERDOSAGE

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.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

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

Inform patients that HBV reactivation can occur in patients coinfected 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 *[see Warnings and Precautions]*.

Drug Interactions

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 *[see Contraindications, Warnings and Precautions and Drug Interactions]*.

Administration

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.

If a dose is missed and it is:

- 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.

Manufactured by AbbVie Inc., North Chicago, IL 60064

Ref: 03-B632 Revised: December, 2017

46A-1937720 **MASTER**

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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.

INDICATION[1]

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 INFORMATION[1]

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 coinfected 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 coinfected 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.

CONTRAINDICATIONS[1]

MAVYRET is contraindicated:

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

WARNINGS AND PRECAUTIONS[1]

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[1]

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.