Opioid-Induced Constipation: Associated Costs of Care and Length of Hospitalization

Osteoporosis in the Managed Care Setting: A Rising Challenge with Growing Treatment Opportunities

Star Ratings and Quality Improvement: Forecasted Measures for 2019 and Program Successes

Variable Fee Schedule Reimbursement: Impact on Antiemetic Utilization and Quality of Care

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Fall 2017

CAR-T and Gene Therapies:

Hope Is on the Horizon

Magellan Rx MANAGEMENT℠

magellanrx.com

RETINAL DISEASES CAN HAVE A BIG EFFECT ON VISION

See for yourself what it's like in **virtual reality**

In My Eyes by REGENERON

Download the free app at **InMyEyesApp.com**.

Doctor-recommended screening, diagnosis, and potential treatment are important for your members with Wet AMD, Macular Edema following RVO, DME, and DR in Patients with DME.* Otherwise, these members may be facing serious risk of vision loss, which may require ongoing resources.[1-3]

THERE'S EYLEA—A treatment option that can fit your plan

- **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**[4]
- **With monthly and every-other-month dosing,† EYLEA offers flexible dosing options to help meet the needs of your providers and your members**[4]

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 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.

†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. **4.** EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. October 2016.

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

EYLEA® (aflibercept) Injection
For Intravitreal Injection

REGENERON

04/2017
US-LEA-13814

EYLEA® (aflibercept) Injection For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of:

- **Neovascular (Wet) Age-Related Macular Degeneration (AMD)**
- **Macular Edema Following Retinal Vein Occlusion (RVO)**
- **Diabetic Macular Edema (DME)**
- **Diabetic Retinopathy (DR) in Patients with DME**

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or 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 (6.1)*]. 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 (2.7) and Patient Counseling Information (17)*].

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 (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

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 potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

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.

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 (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

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REGENERON

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 fall issue of the Magellan Rx™ Report! This issue is packed with lots of great content we think you'll enjoy.

In this issue of the Magellan Rx™ Report, we feature two hot topics: CAR-T therapy and gene therapy. The CAR-T therapy article explains what CAR-T therapy is and how it works; highlights the recent Food and Drug Administration (FDA) approval of the first CAR-T therapy in the U.S.; lists the various investigational agents in development; and discusses the managed care implications of potential FDA approvals of these promising therapies. In the gene therapy article, we review the differences between the two therapies, which are commonly, but incorrectly, considered the same type of therapy.

The gene therapy article, presented in Q&A style, lists many of the important questions payors need to ask as we prepare for the potential approval of the first gene therapy in the U.S. Some of these questions include the following:

- Will gene therapy provide a "one-and-done" cure or will re-treatment be necessary later on?
- How will plans pay for these very expensive and potentially life-saving therapies?
- Who should pay for these treatments if patients are switching between plans?
- Will gene therapy fall under the pharmacy or medical benefit?
- And many more!

A third article presents the results of a retrospective analysis which evaluated the impact of opioid-induced constipation on healthcare costs and utilization in the inpatient setting and discusses the importance of improved clinical management in this area.

Other notable topics discussed in this issue include osteoporosis, Star Ratings and Quality Improvement programs, variable fee schedule reimbursement for chemotherapy-induced nausea and vomiting treatments, a clinical contraceptive program, an update on the hepatitis C virus treatment landscape, investigational treatments for psoriasis, and pipeline biologics in asthma.

In the osteoporosis article, we highlight pipeline agents in development and explain the implications on managed care. The Star Ratings article discusses new measures and shares the results of successful quality improvement programs. The variable fee schedule reimbursement article presents the results of a retrospective study that evaluated the impact of variable fee schedule reimbursement on intravenous 5-HT3 receptor antagonist utilization in adult patients receiving moderately emetogenic or highly emetogenic chemotherapy. In the clinical contraceptive program article, we share the details of a comprehensive contraceptive educational outreach program designed to improve appropriate utilization of all contraceptive therapies.

The hepatitis C update highlights recent changes to the hepatitis C treatment landscape and reviews the differences among available therapies. In the psoriasis and asthma articles, we review various pipeline agents in development that payors should keep a watchful eye on in the coming months, as these agents represent potentially transformative therapies that could result in major shifts in disease management for these patient groups.

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

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

Sincerely,

Mostafa Kamal
Chief Executive Officer
Magellan Rx Management

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Managed Care Newsstand

FDA to Address Orphan Drug Designation Backlog

In June, the U.S. Food and Drug Administration (FDA) announced its plan to address the backlog of orphan drug designation requests to ensure timely responses to future requests and comply with deadlines.

The Orphan Drug Act authorizes the Orphan Drug Designation program to provide orphan status to drugs and biologics intended for safe and effective treatment, diagnosis, or prevention of rare diseases. Perks of orphan designation include tax credits for clinical trial costs, relief from prescription drug user fees if the indication is for a rare disease or condition, and eligibility for seven years of marketing exclusivity upon approval.

With around 200 pending orphan drug designation requests, the FDA has received a steadily increasing number of requests over the past five years. In 2016 alone, 568 new requests were submitted, doubling from 2012. While the increasing number of requests is a positive for sufferers of rare diseases, it presents a unique challenge for the agency.

The plan to eliminate the backlog is a phase of the FDA's new Medical Innovation Development Plan, under which the FDA will aim to support the development of safe, effective, and transformative medical innovations. In an effort to target the orphan drug designation backlog, the FDA will deploy a Backlog SWAT team, including senior, experienced reviewers, to focus solely on the backlogged applications, working from oldest to newest requests. The multifaceted approach, which will be utilized in an effort to ensure all requests receive a response within the promised 90-day window, will include:

- "Reorganizing the review staff to maximize expertise and improve workload efficiencies;
- Better leveraging the expertise across the FDA's medical product centers; and
- Establishing a new FDA Orphan Products Council that will help address scientific and regulatory issues to ensure the agency is applying a consistent approach to regulating orphan drug products and reviewing designation requests."

With a proposed successful elimination date of mid-September, the number and array of orphan drug products available on the market could potentially increase quickly, perhaps changing the landscape of rare disease treatment.

Source:
U.S. Food and Drug Administration. FDA unveils plan to eliminate orphan drug designation backlog. News release. 2017 Jun 29. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm565148.htm. Accessed 2017 Jul 3.

Genetic Testing Cost-Savings System Launched by Anthem Blue Cross

In August, Anthem Blue Cross announced the launch of the Genetic Testing Solution, a provider tool that streamlines approvals for genetic tests. The tool is intended to improve patient access to "the most effective and efficient genetic testing options while decreasing costs in this emerging diagnostic field" and "provide physicians with education to better understand the clinical and financial aspects of genetic testing." The tool may also be of use to payors by speeding up approvals and claims processing times and reducing errors and inefficiencies.

In a press release, Razia Hashmi, MPH, medical director for commercial business at Anthem, stated, "Staying current with all the advances in genetic testing is really confounding for physicians. With the health care community focused on disease prediction, detection, and prevention, it's more important than ever to empower providers with the best information possible about genetic testing so they can help their patients make informed decisions about their health care." The launch of this new tool is timely given that there are more than 70,000 genetic testing products available in today's market, and 10 new products are announced each day.

The launch of this new tool is timely given that there are more than 70,000 genetic testing products available in today's market, and 10 new products are announced each day.

Source:
Anthem Blue Cross announces genetic testing cost-savings system. Managed Health Care Connect. 2017 Aug 3. http://www.managedhealthcareconnect.com/content/anthem-blue-cross-announces-genetic-testing-cost-savings-system. Accessed 2017 Aug 8.

Magellan Rx Management-Health New England Collaboration: Hemophilia Management Program

Hemophilia, a rare genetic bleeding disorder, represents a costly and difficult-to-manage condition. Average annual costs for patients with hemophilia can exceed $250,000 per patient and can be as high as $1 million for patients who have developed inhibitors. Magellan Rx Management and Health New England, a nonprofit health plan client with commercial, Medicare, and Medicaid lines of business, have collaborated to launch a hemophilia management program. The hemophilia utilization management program aims to improve overall quality of care while reducing unnecessary costs under both the pharmacy and medical benefits by:

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

The clinical pharmacist-led program will involve collaboration between pharmacists, hemophilia treatment centers, and pharmacies at various stages throughout the drug delivery process with the aim of improving care coordination and ensuring that program goals are met. The clinical pharmacists will provide monthly communication regarding key clinical information and program outcomes with stakeholders.

Dr. Maria Lopes, chief medical officer of Magellan Rx Management, commented, "Variability in dosing of hemophilia products contributes to increasingly high costs in the hemophilia category. Standardized dosing protocols can significantly reduce potential over-utilization of hemophilia drugs without compromising clinical outcomes. Transparency and care coordination are also key to ensuring that hemophilia patients receive best-in-class care; therefore, it is imperative that important clinical information used to determine optimal outcomes is shared between all stakeholders, including the prescriber, payer, patient, and pharmacy."

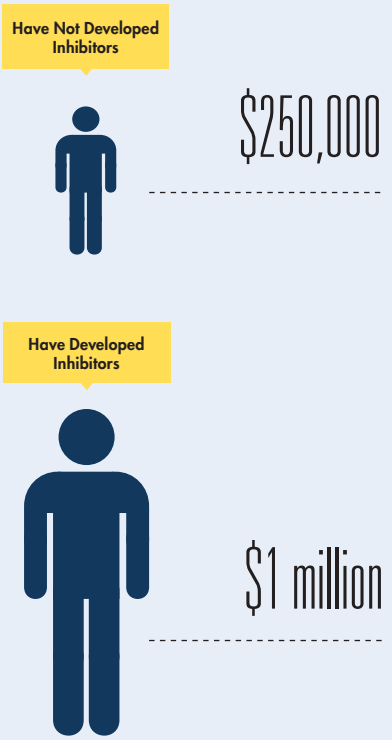
The pharmacy director of Health New England, Andrew J. Colby, RPh, added, "Variability of care and lack of transparency have been prevalent issues for the management of hemophilia members for a long time. By working with Magellan, we anticipate meaningful outcomes from both a quality and a financial perspective by standardizing treatment expectations for all stakeholders. Our goal is to ensure patients with hemophilia are receiving the highest quality of care, while minimizing potential waste created through excess dispensing and inappropriate dosing."

Following program execution, the results of this new hemophilia management program will be shared in an upcoming issue of the Magellan Rx Report™.

Source:
Magellan Rx Management collaborates with Health New England to launch new hemophilia management program. Magellan Health Inc. Press release. 2017 Aug 1. http://ir.magellanhealth.com/releasedetail.cfm?ReleaseID=1035236. Accessed 2017 Aug 8.

AVERAGE ANNUAL COSTS FOR PATIENTS WITH HEMOPHILIA

Average annual costs for patients with hemophilia can exceed $250,000 per patient and can be as high as $1 million for patients who have developed inhibitors.



CAR-T Therapy:

Hope on the Horizon for Cancer Treatment

Hematological malignancy is a term used to describe a malignancy originating in bone marrow cells or the lymphatic system.[1] In the U.S., someone is diagnosed with a hematologic malignancy every three minutes.[2] In addition to the considerable morbidity associated with hematological malignancies, the cost of cancer treatment in the U.S. has increased dramatically over the past 20 years.

Joseph Mikhael MD, MEd, FRCPC
Professor of Medicine,
Consultant Hematologist,
Mayo Clinic Arizona

Prior to the year 2000, the average annual cost of a cancer drug was $5,000 to $10,000.[3] In 2014, almost every newly approved cancer drug had an annual cost of $120,000 to $170,000.[3] Cancer also results in a significant economic burden on society due to lost productivity of the individual diagnosed and the additional healthcare costs that result in increased insurance premiums.[4] When hematological malignancies affect children and adolescents, caregivers may be unable to work as they care for their child.[5]

Hematological malignancies are often grouped into three subtypes: leukemias, lymphomas (Hodgkin lymphoma [HL], non-Hodgkin lymphoma [NHL]), and plasma cell neoplasms (multiple myeloma [MM]).[1,6] The exact incidence and prevalence of hematological malignancy are difficult to measure, as the diagnosis is often challenging and complex. Diagnosis commonly requires the use of a variety of tools, such as histology, cytology, immunophenotyping, cytogenetics, imaging, and clinical data.

Leukemia occurs secondary to the overproduction of abnormal white blood cells by the bone marrow and is classified as myeloid or lymphatic based on the type of white blood cell that is affected.[7] Leukemia accounts for 2.5% of all cancers worldwide, with 250,000 people diagnosed annually.[1] Although leukemia may affect individuals of any age, more than half of cases occur in adults 65 years of age and older, with the median age of diagnosis being 67 years according to U.S. Surveillance, Epidemiology, and End Results Program registries.[1] Although older adults are most commonly affected, leukemia accounts for approximately 35% of cancers in children younger than 14 years of age.[1]

Lymphoma originates in the lymphatic system and causes the uncontrolled growth of malignant white blood cells that ultimately form tumors in the lymph nodes.[1] Lymphoma can be further divided into two subtypes, including HL and NHL, based on whether the cancer involves the Reed-Sternberg cells.[1,8] HL, the less common form of lymphoma, involves the Reed-Sternberg cells, while any lymphoma not involving the Reed-Sternberg cells would be classified as NHL.[8,9] HL may occur at any age; however,

it most commonly occurs in early adulthood (age 25 to 30) and late adulthood (after age 55).[1] NHL is the most common cancer of the lymphatic system, with 65,000 cases diagnosed in the U.S. each year.[10] Of note, the incidence of NHL has increased dramatically in the past 50 years, with the incidence rate nearly doubling since the early 1970s.[10] It is possible that this increase may be attributed in part to improvements in detection and diagnosis; however, the cause of this increasing trend is largely unknown.

Myeloma develops as a result of the accumulation of abnormal antibody-producing white blood cells in the bone marrow, known as plasma cells.[11] More than 10,000 myeloma-related deaths occur in the U.S. annually and more than 20,000 new cases are diagnosed each year.[12] Myeloma has the lowest five-year survival rate of the main types of hematological malignancies at approximately 38.5% (compared to 55% for leukemia and 68% to 85% for lymphoma).[12]

CAR-T Therapy: A Potential Disruption to the Current Treatment Landscape

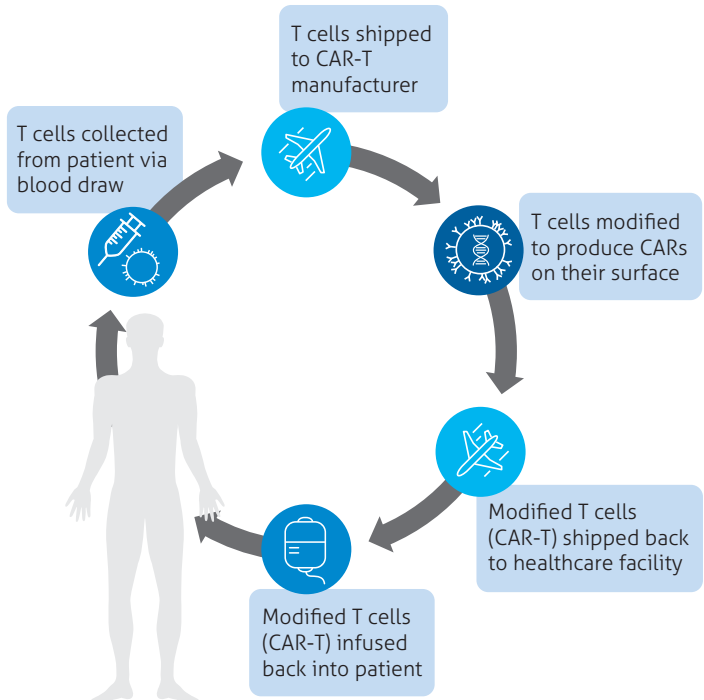
The treatment approach for hematological malignancies varies based on the specific subtype of malignancy as well as patient-specific factors, such as age, health status, stage, and the presence of any cytogenetic abnormalities.[7,8,13] Treatment also often incorporates several modalities, including chemotherapy, radiation, stem cell transplant, targeted treatments, and immunotherapies such as monoclonal antibodies.[7,8,13] The majority of patients will receive chemotherapy at some point during the course of their treatment, based on the type and subtype of malignancy that is being treated.[7,8,13] There has been an increasing use of novel biological approaches of late, with a particular interest in immunotherapies, whereby the patient's immune system is employed against the cancer.

As the approach to the treatment of hematological malignancies has become increasingly sophisticated with the advent of immunotherapy and targeted therapy, researchers are now exploring an exciting new technology capable of rewiring the body's own immune system to fight cancer. Chimeric antigen receptor T-cell (CAR-T) therapy is a highly personalized approach to oncologic immunotherapy that involves the extraction of T-cells from the patient's blood. These T-cells are then engineered in a laboratory, adding chimeric antigen receptors (CARs) to the T-cells, which will facilitate their attachment to cancer cells. The altered T-cells are then multiplied in the laboratory and reinfused into the patient's blood where they can recognize and attack the cancer cells.[14-16] CAR-T cells may also remain in the body long after reinfusion, which theoretically may guard against recurrence and allow for long-term remission.[17]

In early clinical trials, CAR-T therapies have been associated with remission rates of up to 94%.[14] This is particularly significant because the majority of these trials studied CAR-T therapy in patients who had failed treatment with all available therapies for their cancer.[14,15] CAR-T therapy has been studied across a variety of hematological malignancies, including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, types of NHL (including diffuse large B cell lymphoma [DLBCL] and follicular lymphoma), and multiple myeloma.

Although early clinical trial success has some calling CAR-T therapy a "miracle cure," there are serious safety concerns associated with treatment, including cytokine release syndrome (CRS), B-cell aplasia, and tumor lysis syndrome (TLS). When the immune system is activated by CAR-T therapy, an increased number of cytokines are produced, which may lead to CRS. CRS usually occurs within one week of treatment and the symptoms — which may include high fever, hypotension, poor lung oxygenation, delirium, confusion, and seizures — are usually reversible.[17] CRS can be treated with tocilizumab, which represents a very effective, but expensive, treatment option.[18]

Another potential side effect of CAR-T therapy, B-cell aplasia, may occur when the engineered CAR-T cells target normal B cells in addition to the cancerous B cells.[17] The depletion of B cells may result in an impaired immune response; however, administration of immunoglobulin may be used to help prevent infection.[17] Arguably the most severe potential side effect is TLS, which encompasses a variety of metabolic complications that may occur secondary to the breakdown of



dying cells. TLS may occur shortly after treatment or may be delayed, occurring one month post-treatment or later, and may be life-threatening.[17] It should be noted that this side effect is not specific to CAR-T therapy and may occur with any treatment that results in the breakdown of cancer cells.

While it has been a race to bring the first CAR-T therapy to market, tisagenlecleucel (KYMRIAH™, Novartis) won the race and received the first Food and Drug Administration (FDA) approval for a CAR-T therapy. Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.[20] Axicabtagene ciloleucel (Kite Pharma Inc.) is currently under review by the FDA for the treatment of relapsed or refractory aggressive NHL in patients who are ineligible for autologous stem cell transplant, and a decision is expected on November 29, 2017.[20] Although these agents may receive initial approval for different cancer types, there will likely be some overlap with expanded indications in their future, including DLBCL (a type of NHL), an investigational indication for which both agents have been granted the breakthrough therapy designation by the FDA.[21,22]

Tisagenlecleucel

The FDA approval of tisagenlecleucel was based on data from the phase II ELIANA study (N=88) in which 83% of patients achieved complete remission or complete remission with incomplete blood count recovery three months after CAR-T cell infusion.[23] Of those who achieved complete remission, no minimal residual disease was detected.[23] Furthermore, the relapse-free survival rate among responders after remission onset was 75% (95% confidence interval [CI], 57 to 87%; median duration of response not reached) at six months and 64% (95% CI, 42 to 79%) at 12 months.[23] Grade 3 or 4 CRS was observed in 47% of patients enrolled in the trial; and grade 3 neurological and psychiatric events, including encephalopathy and delirium, were observed in 15% of patients. On July 12, 2017, the FDA Oncologic Drugs Advisory Committee voted unanimously (10 to 0) in favor of approval of tisagenlecleucel for the treatment of children and young adults with relapsed or refractory B-cell ALL.[24] Novartis has indicated that a supplemental biologics license application (BLA) submission for the treatment of adults with relapsed or refractory DLBCL is planned for later in 2017.[24]

Axicabtagene Ciloleucel

The BLA submission for axicabtagene ciloleucel was based on data from the phase II ZUMA-1 trial (N=101) in which 82% of patients achieved an objective response (P<0.0001).[20] After a median follow-up of 8.7 months, 44% of patients were having an ongoing response to therapy, including 39% who had a complete response.[20] Although the median overall survival had not yet been reached at follow-up, in the SCHOLAR-1 study, a similar patient population achieved a median overall survival of approximately 6.6 months.[20] Grade 3 or 4 CRS was observed in 13% of patients, and neurologic adverse events were observed in 28% of patients. Of note, three deaths did occur during the study, two of which were determined to be related to the study drug.[25] One patient death was due to hemophagocytic lymphohistiocytosis, another was due to cardiac arrest secondary to CRS, and the third was due to cerebral edema.[25]

The clinical program for a third CAR-T candidate, JCAR015 from Juno Therapeutics, was discontinued in March 2017 after serious safety concerns arose in clinical trials.[26] The pivotal phase II ROCKET trial, which was placed on clinical hold twice due to safety concerns, enrolled 38 patients with relapsed or refractory B-cell ALL, five of whom died over the course of the study.[26] As the CEO of Juno pointed out in a statement issued by the company, the death rate in the ROCKET trial was 13%, which is in line with other CAR-T trials of adults with late-stage ALL. The concerning aspect is that all five deaths were related to cerebral edema, an adverse effect that had not been observed with other CAR-T therapies to date.[26,27]

Although CAR-T therapy may bring hope to those who have exhausted all available treatment options, there are some significant potential barriers to the widespread uptake of these agents once they hit the market. CAR-T therapy is created from the individual patient's own T-cells through a complex process that takes time. Once the T-cells are removed from the patient, they must be cryopreserved and shipped to a facility where they are genetically modified and manufactured in a laboratory. The cells must then be shipped back to be infused into the patient. Novartis indicated that they are working toward a turnaround time of approximately 22 days at the time of commercial launch, anticipating that 10 to 12 days will be required for actual cell processing.[28] Kite has indicated that they are aiming for a shorter turnaround time of 16 to 18 days, requiring six or seven days for cell processing.[28] Novartis has commented that the company is confident they will be able to meet the necessary manufacturing demands in the near future through continuous process improvements.[28]

In addition to the logistical issues, there are also concerns about the high costs. Following FDA approval of tisagenlecleucel, Novartis announced that its CAR-T therapy would be priced at $475,000 for a single infusion.[29] This price tag may be lower than what had been anticipated based on Novartis' previous indication that the price of stem cell treatment, which can cost as much as $800,000, may offer a benchmark.[28] The National Institute for Health and Care Excellence recently conducted a mock technology appraisal analysis that determined that $649,000 for CAR-T therapy would be justified for young patients with ALL.[30] Jefferies analysts suggest that these findings may have been influenced by the younger age group being evaluated and that an older population may have produced a lower price.[30] Although Kite has not provided details on its pricing strategy, Jefferies analysts' current cost estimate is that axicabtagene ciloleucel may come to market at approximately $300,000 per patient.[30]

Implications for Managed Care

Despite the unanswered questions surrounding CAR-T therapy, it is clear that payors will soon face significant challenges in managing these agents. In addition to the high cost of engineering CAR-T cells, it is likely that there will be significant medical costs associated with the management of adverse effects, such as CRS. It is also likely that these agents will need to be administered at infusion centers that specialize in CAR-T therapy because of the risks associated with treatment.[31] To minimize unnecessary risk and ensure the best outcomes for their members, payors should consider restricting CAR-T therapy to a limited network of specialized infusion centers.[31]

Although the initial approval of tisagenlecleucel and potential approval of axicabtagene ciloleucel may be for the treatment of a relatively small population, we may expect to see some interest in using these agents across broader indications based on their mechanisms of action. It will be critical for payors to remain abreast of ongoing clinical trials and available data to ensure that their management strategies allow for the use of CAR-T therapies in only the most appropriate patient groups.[31]

Given the high cost of these agents, payors should consider additional cost-containment strategies, such as engaging in pay-for-performance agreements, where a portion of the cost of therapy may be reimbursed if the patient does not achieve the desired outcome. This type of risk-sharing agreement may allow payors to provide these potentially life-saving treatments to a greater number of patients who need them.[32]

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Gene Therapy:

Payor Considerations for These Genetic Breakthroughs

Imagine a world where devastating diagnoses like human immunodeficiency virus, hemophilia, sickle-cell anemia, spinal muscular atrophy, and congenital blindness are not diseases to be managed, but diseases that can be erased using gene therapy.[1] It almost sounds too good to be true, but thanks to advances in modern medicine, such a world may soon exist.[2] Almost 30 years after the first gene therapy was tested in humans, we may be only months away from the first gene therapy to be approved in the U.S.[3]

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As the Food and Drug Administration (FDA) approvals for gene therapy come pouring in, payors will be faced with unprecedented challenges in managing this new area of medicine.

What is gene therapy and how does it work?

The American Society of Gene & Cell Therapy defines gene therapy as the use of genetic material to manipulate a patient's cells to treat an inherited or acquired disease.[3] Genetic material that is inserted directly into the cell is typically not functional and may include nucleic acids, viruses, or genetically engineered microorganisms.[4] As such, a genetically engineered vector is used to deliver the gene. One of the most efficient vectors discovered to date is a virus; modified viruses are able to insert genetic material into the cell by infecting the cell, but the modifications prevent that virus from causing disease in the human host.[5] Commonly utilized viruses include retroviruses and adenoviruses; retroviruses are able to integrate their genetic material into a chromosome in the human cell, while adenoviruses introduce deoxyribonucleic acid (DNA) into the nucleus of the cell but not into the chromosome.[5]

Is gene therapy the same as genome editing and CAR-T therapy?

In short, no; however, many individuals confuse the three therapeutic approaches. Genome editing refers to the alteration of a specific DNA sequence within a living cell by cutting a strand of DNA at a specific point, allowing intrinsic cellular repair mechanisms to fix the broken strands, and thereby allowing the repaired strands to affect gene function.[6] Recombinant adeno-associated viruses (rAAV) insert, delete, or replace DNA sequences in cells using an exchange of nucleotide sequences.[1] The rAAV platform is able to affect the DNA sequences in cells without causing a double-stranded DNA break, making it nonpathogenic and ideal for gene therapy in humans.[1] Gene editing using the rAAV platform is very precise; homologous recombination allows for the editing of the cell down to the level of a single base pair without sequence error.[7]

The clustered regularly interspaced short palindromic repeat (CRISPR) associated system technology, more commonly known as CRISPR-Cas9, more recently became the popular gene-editing technique of choice due to its precision in editing any DNA, bacterial or human, as well as its relative low cost compared to older methods.[8,9] Heralded as Science magazine's 2015 Breakthrough of the Year, CRISPR-Cas9 contains two basic components: the guide ribonucleic acid (RNA) that is used to target the specific DNA sequence and Cas9, the enzyme or nuclease that cuts the targeted DNA.[10] The result is a highly accurate double-stranded break in DNA, following which the gene can be edited with surgical precision to correct dysfunctional genes.[11] In mouse models, scientists have used CRISPR-Cas9 technology to successfully correct the genetic mutation responsible for cataracts. Furthermore, using primary adult intestinal stem cells cultured from patients with cystic fibrosis, CRISPR-Cas9 technology was used to correct the cystic fibrosis transmembrane conductance regulator locus responsible for causing cystic fibrosis.[11]

Discussed in further detail on page 7, chimeric antigen receptor T-cell (CAR-T) therapy represents another significant development that is frequently, albeit incorrectly, referred to as gene therapy. CAR-T therapy involves the extraction of T-cells from the patient's blood, followed by the genetic manipulation of those cells in the laboratory and the reinfusion of the genetically modified cells back into the patient's bloodstream, where they target and attack cancerous cells.[12,13] There are several CAR-T therapies in late-stage development that are being studied for their role in treating various hematological malignancies, which will be discussed in a separate article featured in this issue of the Magellan Rx Report™.[14]

If gene therapy has been around for 30 years, why has it not reached the U.S. market yet?

A potentially obvious answer to this question is that gene therapy is very complex and the process of editing the human genome is very difficult. For some targeted disease states, a very large number of manipulated cells would be required to achieve the desired outcome. The gene must also be delivered to a precise location — delivery to the incorrect cell or the incorrect tissue could be catastrophic. Once delivered to the correct location, the gene must be activated and remain activated in order to achieve the desired outcome. In the early 2000s, the investigators of two trials studying gene therapy in children with X-linked severe combined immunodeficiency (SCID) discovered how catastrophic the consequences could be if the delivery of the gene therapy is less than precise.[15] The therapy being studied was intended to restore the function of the gamma c gene in immune cells and it appeared to be very effective, restoring immune function to the majority of study subjects.[15] Despite what appeared to be very successful treatment of SCID, five patients later developed leukemia.[15] Upon further investigation, it was discovered that the gamma c gene that was introduced had attached to a gene that regulates the rate of cell division.[15] As a result of this discovery, researchers have developed vectors that are capable of targeting DNA integration to lower-risk locations in the genome where they are less likely to interfere with the normal function of other genes.[15]

Researchers have developed vectors that are capable of targeting DNA integration to lower-risk locations in the genome where they are less likely to interfere with the normal function of other genes.

Another challenge in the development of gene therapy has been the human body itself. The immune system is very proficient at combating foreign invaders, including bacteria and viruses. This obstacle poses a significant problem for a technology based on the introduction of foreign vectors into the body. Although gene therapy has been studied since the 1990s, the field of study suffered a major setback following the tragic death of a patient with a rare liver disorder in 1999.[15] Following the administration of an experimental dose of adenovirus vector, the patient developed complications secondary to his body's inflammatory immune response.[15]

As this case highlights, it is essential for the gene delivery vector to avoid the immune surveillance system. Some strategies that may be used include delivering the virus to the cell outside of the patient's body, giving patients immunosuppressants to temporarily suppress the immune response during treatment, using the lowest possible dose of virus that maintains efficacy, and using vectors that are less likely to trigger an immune response whenever possible.[15]

What gene therapies are currently in development?

LUXTURNA™ (voretigene neparvovec)

Voretigene neparvovec is an investigational, one-time gene therapy that is being evaluated for the treatment of vision loss due to confirmed biallelic RPE65 mutation-associated retinal disease.[16] Specifically, voretigene neparvovec has been studied in clinical trials in a subset of patients with inherited retinal disease who have Leber congenital amaurosis, which is the most common form.[16,17] Utilizing an adeno-associated virus serotype 2, voretigene neparvovec allows for the introduction of a healthy RPE65 gene into the retina, but would not repair or eliminate the defective gene.[17]

In a phase III trial, 20 patients with confirmed genetic diagnosis of inherited retinal dystrophy with biallelic RPE65 mutation received treatment with voretigene neparvovec.[18] At baseline, patients had best corrected visual acuity of 20/60 or worse in each eye or

visual field less than 20 degrees in any meridian, or both, with sufficient viable retina and the ability to perform standardized multi-luminance mobility testing (MLMT) within the luminance range evaluated.[18] The MLMT evaluates the patient's ability to maneuver through an obstacle course at various light levels.[18] At one year post-treatment, the mean bilateral MLMT change score was 1.8 light levels in the intervention group compared to 0.2 light levels in the control group (difference, 1.6; 95% confidence interval, 0.72 to 2.41; P=0.0013).[18] Of the patients in the intervention group, 65% passed the MLMT at the lowest luminance level tested (1 lux), demonstrating the maximum possible improvement.[18] The improvement in MLMT observed in patients treated with voretigene neparvovec suggests that therapy may be associated with functional improvements in vision, which may allow patients to have greater mobility and independence.[17] In January 2017, the FDA granted a request to expand the previously granted orphan drug designation to also include the treatment of inherited retinal dystrophy due to biallelic RPE65 mutations.[16,17] In May 2017, a rolling biologics license application (BLA) for voretigene neparvovec was submitted to the FDA. The FDA has accepted the BLA submission and granted it priority review, and has assigned a Prescription Drug User Fee Act (PDUFA) date of January 12, 2018.[17] The FDA has also announced a public advisory commitee meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee, slated for October 12, 2017, to discuss and make recommendations for the BLA application for voretigene neparvovec. Additionally, the FDA has designated voretigene neparvovec as a treatment for a rare pediatric disease under the Rare Pediatric Disease Priority Review Voucher program.[17]

Fitusiran

Fitusiran is an investigational RNA interference (RNAi) therapeutic being studied for the treatment of hemophilia A and B, with or without inhibitors.[19] Fitusiran works by targeting and lowering antithrombin levels, thus promoting sufficient production of thrombin upon activation of the clotting cascade, ultimately restoring hemostasis and preventing bleeds.[19]

In the phase II OLE study (N=33), patients with hemophilia A or B, with or without inhibitors, received treatment with fitusiran via once-monthly, low-volume subcutaneous injection.[19] Patients treated with fitusiran achieved increases in thrombin production as well as reductions in antithrombin approaching 80%.[19] At baseline, patients reported a median of 20 bleeding events annually; following treatment initiation, a median of one bleeding event was observed.[19] Of the harder-to-treat patients with inhibitors (N=14), 64% of patients have not bled since starting treatment with fitusiran.[19] Notably, there were no thromboembolic events, laboratory evidence of pathological clot formation, or instances of anti-drug antibody reported during the study.[19] Fitusiran may be used in conjunction with blood replacement factor; however, based on clinical trial data, it may reduce the frequency of replacement factor administration.[19] The phase III ATLAS clinical program was initiated in July 2017, with initial results anticipated in mid-to-late 2019.[19]

However, the manufacturer recently announced that it has suspending dosing in all ongoing fitusiran studies based on the occurrence of a fatal thrombotic event in a patient with hemophilia A without inhibitors in the phase II OLE study.[20] The manufacturer has stated that it aims to resume dosing as soon as possible upon agreements with authorities and appropriate protocol amendments.[20]

Fitusiran differs slightly from other gene therapies in that it requires an ongoing subcutaneous injection once monthly to ensure adequate thrombin levels are maintained to prevent bleeding episodes in patients with hemophilia.

ABO-201

ABO-201 is an AAV-based one-time intravenous gene therapy in development for the treatment of juvenile Batten disease.[21] Awarded the orphan drug designation by the FDA in June 2017, ABO-201 works by introducing a functional copy of the defective CLN3 gene to cells within the central nervous system with the goal of reversing the effects of the genetic errors that cause juvenile Batten disease.[21] Human trials are expected to begin in late 2017.[21]

Will gene therapy provide a "one-and-done" cure or will re-treatment be necessary later on?

Whether a gene therapy will require a single dose or multiple doses will depend on the specific therapy and disease state being targeted; however, many of the agents in development are for one-time administration, including voretigene neparvovec and ABO-201.[16,21] Fitusiran differs slightly from other gene therapies in that it requires an ongoing subcutaneous injection once monthly to ensure adequate thrombin levels are maintained to prevent bleeding episodes in patients with hemophilia.[19]

How much will gene therapy cost?

Although the exact cost of gene therapy is largely unknown at this time, there is one thing we can be reasonably sure of: it will be very expensive. In 2012, Glybera® (alipogene tiparvovec) was granted European Medicines Agency approval for the treatment of ultra-rare hereditary lipoprotein lipase deficiency (LPLD), making it the first gene therapy to be approved for use in humans.[22] Glybera® came to market with a price set at $1 million per patient, which proved to be more than payors were willing

and able to pay.[22] After five years on the market and only one patient approved for use, Glybera® was ultimately pulled from the market in 2017.[22] Although Glybera® was never subjected to payor pressure in the U.S. market, it would be fair to assume that such a costly gene therapy would receive very similar pressure in the U.S.[22,23] Gene therapy is also set to enter the U.S. market when outrage over the cost of prescription drugs is at an all-time high.[24] Drug makers will need to carefully consider the value of their therapy in the context of what cost the market can reasonably tolerate.[24]

Although we have even less information regarding the potential cost of voretigene neparvovec, analysts estimate global sales of $573 million in 2023.[25] In a draft scoping document released by the Institute for Clinical and Economic Review, it is estimated that the cost per patient for voretigene neparvovec may be between $650,000 and $1 million based on the cost of other gene therapies that have come to market in Europe.[16] In an article by Alissa Fleck for BioPharm Insight, it is suggested that payors may be unlikely to pay "much more" than $1.5 million per patient.[25]

How will plans pay for these very expensive and potentially life-saving therapies?

As mentioned previously, one of the biggest challenges facing payors will be the extremely high up-front cost associated with gene therapy. This scenario is not new — a similar issue arose with the advent of new direct-acting antivirals for the treatment of the hepatitis C virus (HCV).[26] Despite the ability of these new agents to cure the disease and avoiding significant costs related to hospitalizations, liver transplants, and cancer, the immediate cost and sheer number of patients awaiting treatment overwhelmed the healthcare system.[26] As a result, many payors had to make difficult decisions about which patients should be treated and when to ensure that they were able to treat the sickest patients first while remaining in business.[26]

Gene therapies may pose a similar problem — although the patient pool for a given gene therapy may be much smaller compared to HCV, the extremely high cost of these therapies will make it difficult for payors to provide treatment to those who need it.[26] One potential solution that has been discussed is using an amortized payment plan that would allow payors to spread out the cost of gene therapy over several years.[26] Although this option may alleviate some of the immediate burden, it may be an important consideration for patients who switch plans (discussed further below).[26]

Another potential solution is the use of pay-for-performance contracting. This approach would put some of the responsibility back on the manufacturer; if the gene therapy does not yield the desired outcome, the manufacturer would have to reimburse some or all of the cost of therapy based on the terms that had been negotiated. For this to work, the manufacturer and payor must agree on what the desired outcome is, how treatment success will be measured, and what the value of successful treatment would be.[26,27]

Given that gene therapy will pose a significant up-front cost to the payor, it is important to consider the potential "return on investment" from a payor perspective.

Who should pay for these treatments if patients are switching between plans?

Given that gene therapy will pose a significant up-front cost to the payor, it is important to consider the potential "return on investment" from a payor perspective. Using the example of the new direct-acting HCV antivirals, a payor might expect to have significant cost savings in the long term by avoiding a liver transplant if a patient is successfully cured; however, what happens if that patient switches plans one year after they are cured of HCV? As mentioned previously, manufacturers and payors alike are considering payment plans and pay-for-performance contracts to help lessen the financial burden of gene therapy.[28] In these negotiations, consideration may be given to the potential forgiveness of outstanding payments if a patient switches plans within a certain period of time.[29]

Will gene therapy fall under the pharmacy or medical benefit?

Whether a gene therapy is considered a pharmacy or medical benefit will likely vary depending on the specific therapy in question. Because many gene therapies have complex manufacturing processes and/or require administration by a trained healthcare professional, it is likely that many gene therapies would fall under the medical benefit. As gene therapy becomes more efficient, it is possible that we will see more off-the-shelf therapies that could be filled at the pharmacy and be considered a pharmacy benefit.

How will payors determine the value of gene therapy?

As mentioned previously, determining the value of a given gene therapy will be integral to determining what payors may be willing to pay. The payor should carefully consider the disease state being treated and how it impacts the patient (e.g. impact on quality and duration of life), as well as the anticipated outcome of treatment based on clinical trial data. For example, does the gene therapy improve quality of life marginally, or does it cure disease and reduce mortality risk?

How will payors determine who to treat?

As with any new therapy, the payor should carefully evaluate clinical data to determine which patients would benefit the most from treatment. In situations where the gene therapy is intended for a specific gene mutation, payors should ensure that the patient has received the appropriate genetic testing to confirm

that they would be a candidate for therapy. It is recommended that whenever possible, payors monitor patients who have been treated with gene therapy to determine if the desired outcome has been achieved; this information will not only be important for pay-for-performance deals, but it may also help inform future decisions about coverage of a given therapeutic. In the case of therapeutics that require repeat dosing, monitoring the patient for the desired outcome will help the payor determine if ongoing treatment is appropriate or futile.

Conclusion

While exciting and potentially life-changing in some instances, gene therapy comes with important considerations regarding safety, efficacy, long-term outcomes, and cost. Safety considerations include the use of vectors that target DNA integration to lower-risk locations in the genome and avoid the immune surveillance system. In terms of efficacy and long-term outcomes, many of these questions remain an unknown at this time until more data are available; however, manufacturers are committed to tracking and sharing this information with stakeholders. Additional information about the cost of these therapies will become available as these investigational treatments approach their respective PDUFA dates. Payors should continue to ask these important questions about this innovative therapy until more information is available from manufacturers.

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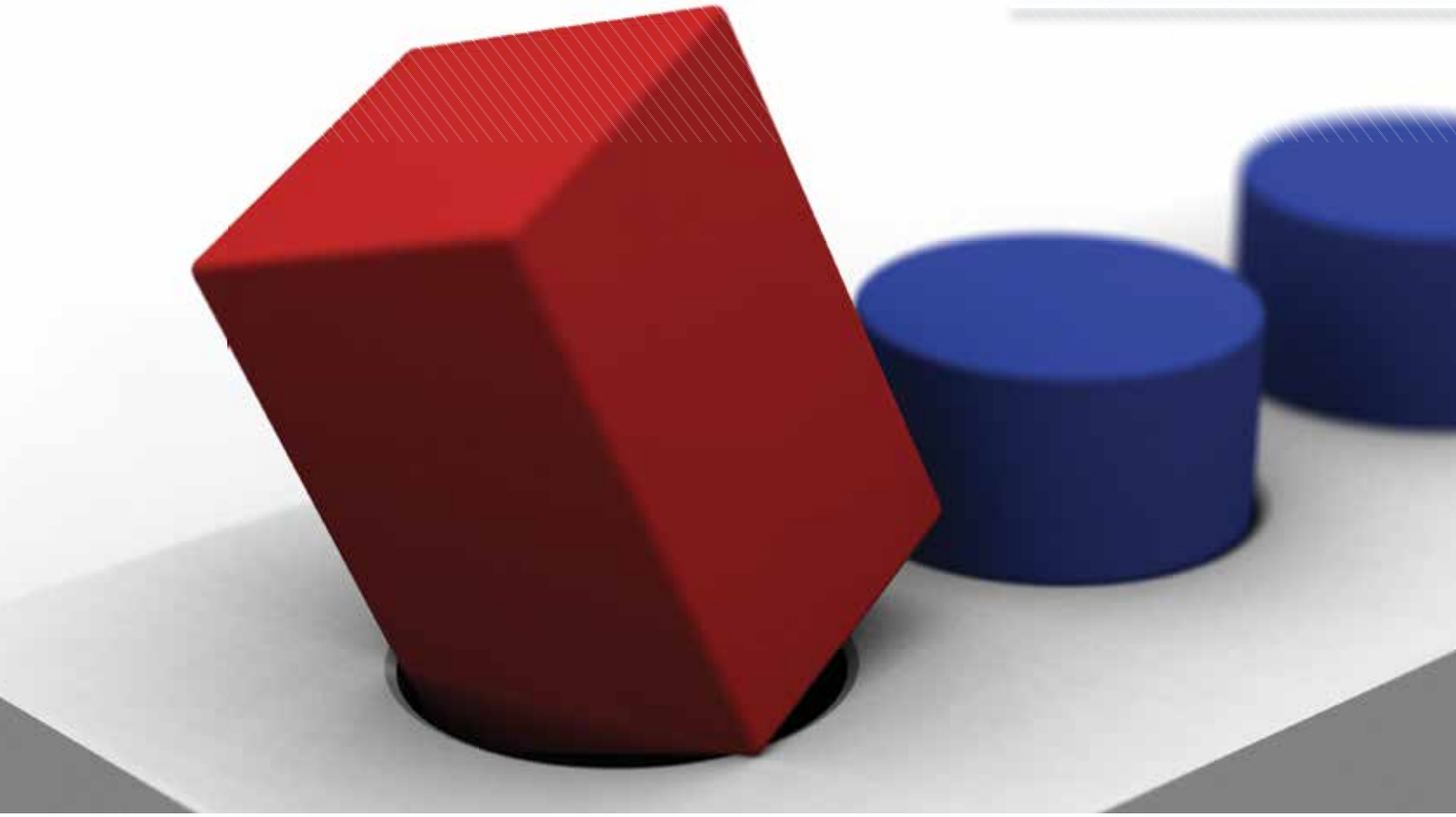

ViiV Healthcare

Opioid-Induced Constipation:

Associated Costs of Care and Length of Hospitalization

Background

Opioids are commonly used in the treatment of chronic pain. Approximately 4% of the U.S. population is taking opioids, primarily for non-cancer pain.[1] In the last decade, the number of prescription opioids dispensed has risen significantly, from nearly 149 million prescriptions in early 2003 to 207 million in 2013.[1] Opioid use is associated with a variety of adverse effects, with constipation being the most common gastrointestinal complaint.[2] When constipation occurs as a result of opioid use, the condition is referred to as opioid-induced constipation (OIC). OIC is defined as "a change, after initiating opioid therapy, from baseline bowel habits that is characterized by any of the following: reduced frequency of spontaneous bowel movements, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency."[1]

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As suggested by a systematic review of randomized trials of opioid use for chronic, non-cancer pain, the prevalence of OIC can be as high as 71%.[3] A second review demonstrated that approximately 40% of patients receiving chronic opioid therapy for non-cancer pain suffer from some degree of bowel dysfunction, including constipation.[4] OIC does not appear to subside with continued exposure to opioid therapy. The burden of OIC is large, affecting overall quality of life, daily activities, work productivity and interfering with pain management.[5,6] Given that OIC is often overlooked by the clinician and yet remains a burden for the patient, this can lead to a decrease in adherence to pain therapy, potentially resulting in ineffective or failed pain management and ultimately, decreased quality of life.[6] OIC can also lead to increased healthcare costs and resource utilization in patients receiving long-term opioid therapy.[5]

Despite the large disease burden and potentially serious consequences, OIC may be largely considered an insignificant and preventable side effect of opioid pain management. This perspective may have led to an underestimation of and underappreciation for the burden and impact of OIC.[7] Although studies have evaluated the implications of opioid use and OIC, these studies generally have been conducted in ambulatory patients, and few studies have analyzed the impact of OIC in the inpatient hospitalization setting. This study aimed to evaluate the impact of OIC on healthcare costs and utilization in the inpatient setting.

Methods

Study Design and Population

This retrospective study was conducted using electronic medical record (EMR) data from a single, regional integrated delivery network (IDN). Specifically, the study considered medication administration records as well as procedure-level billing records for each inpatient

hospital stay. The population consisted of all qualifying patients over 18 years of age, who had an inpatient hospital stay between January 1, 2010, and August 31, 2014, and were administered a traditional opioid or a partial agonist during their hospitalization. No sampling was performed; all patients who met the inclusion criteria were included in the study. Any patients with an existing diagnosis of inflammatory bowel disease, neurogenic bowel, or cancer were excluded from the analysis.

Data Analysis

Subgroups consisting of patients with constipation versus those without constipation were identified for analysis. Patients were considered constipated if there was documentation of a diagnosis code for constipation or a constipation-related procedure or if a laxative was administered more than 24 hours after receiving an opioid. Variables assessed included the following: baseline patient characteristics, opioid utilization, laxative utilization, utilization of products that may contribute to constipation, utilization of procedures used to treat or manage constipation, surgical procedures, total cost of hospital admission, average length of stay (LOS), admission source (emergency department, transfer from another facility, etc.), and discharge status. The primary outcome measures for this study were hospital cost of care and LOS. Additionally, data were further categorized according to clinical classification software for ICD-9 and ICD-10.[8] Descriptive statistics were generated with the mean, standard deviation (SD), and median provided for continuous variables, and frequency and percentage for categorical data. Continuous outcomes between cohorts were compared using t-tests.

Results

Overall

A total of 4,997 patients with a mean age of 53.9 years met the study inclusion criteria. The sample was 53.3% female and 46.7% male (Table 1). A total of 81 clinical classifications, or the reasons for admittance, were represented; however, both patients with and without constipation were represented in only 62 of these clinical classifications.

In the overall population, among patients with constipation, across all clinical classifications, the cost of care was higher by $3,920 per hospitalization and the LOS was about three days longer than the LOS for patients without constipation. About 73% of the clinical classifications displayed a higher cost of care and LOS in patients with constipation when compared to those without constipation. An even higher percentage (86%) of these clinical classifications

TABLE 1. BASELINE CHARACTERISTICS

Baseline Characteristics Total N =4,997			Constipation Status		
			Yes N = 2,696	No N = 2,301	P-value
Age, years mean ± SD [Median]	Continuous	53.91 ± 19.75 [55]	57.73 ± 18.92 [59]	48.06 ± 19.64 [49]	< 0.0001
Age Distribution	18-20	147 (2.9%)	58 (2.2%)	89 (3.9%)	< 0.0001
	21-30	696 (13.9%)	237 (8.8%)	459 (19.9%)	
	31-40	592 (11.8%)	256 (9.5%)	336 (14.6%)	
	41-50	691 (13.8%)	398 (14.8%)	293 (12.7%)	
	51-60	841 (16.8%)	463 (17.2%)	378 (16.4%)	
	61-70	806 (16.1%)	489 (18.1%)	317 (13.8%)	
	71-80	707 (14.1%)	430 (15.9%)	277 (12.0%)	
	81+	517 (10.3%)	365 (13.5%)	152 (6.7%)	
Gender	female	2,665 (53.3%)	1,417 (52.6%)	1,248 (54.2%)	0.353845
	male	2,332 (46.7%)	1,279 (47.4%)	1,053 (45.8%)	

showed longer LOS for patients with constipation.

Table 2 displays the mean costs of care and LOS by clinical classification for patients with and without constipation, the results of which show the overall tendency for OIC to lengthen hospitalization and increase cost of care. Table 2 also includes the overall mean across all clinical classifications, showing that constipation tended to lead to longer hospitalization and higher costs in this population.

In most categories of clinical classifications, the cost of care for patients with constipation was greater than the cost of care for patients without constipation.

TABLE 2. HEALTHCARE RESOURCE UTILIZATION BY CLINICAL CLASSIFICATION

Clinical Classification	Patients With Constipation			Patients Without Constipation		
	Count	Cost of Care Mean ± SD [Median]	Length of Stay Mean ± SD [Median]	Count	Cost of Care Mean ± SD [Median]	Length of Stay Mean ± SD [Median]
Diseases of the heart	104	$35,833 ± $35,381 [$22,901]	8.05 ± 4.56 [6.00]	121	$30,319 ± $26,544 [$24,261]	5.35 ± 6.18 [4.00]
Fractures	99	$39,176 ± $37,390 [$29,872]	9.38 ± 5.77 [7.00]	83	$26,545 ± $24,790 [$18,656]	5.52 ± 7.68 [3.00]
Spondylosis; intervertebral disc disorders; other back conditions	92	$35,903 ± $27,803 [$29,077]	6.15 ± 31.42 [4.00]	121	$27,376 ± $19,317 [$22,440]	5.66 ± 7.03 [2.00]
Nontraumatic joint disorders	54	$22,017 ± $10,033 [$19,807]	4.65 ± 2.63 [3.00]	151	$21,450 ± $13,865 [$19,733]	3.26 ± 3.44 [3.00]
Other injuries/ conditions due to external causes	34	$58,234 ± $60,113 [$42,413]	12.50 ± 8.84 [10.00]	23	$41,456 ± $44,455 [$27,999]	9.09 ± 8.90 [5.00]
Other gastrointestinal disorders	33	$26,661 ± $24,743 [$18,934]	8.67 ± 3.92 [7.00]	22	$17,873 ± $15,591 [$10,859]	5.95 ± 8.06 [5.00]
Other connective tissue disorders	28	$31,373 ± $19,707 [$26,438]	8.14 ± 4.70 [4.50]	65	$24,361 ± $15,661 [$21,866]	4.46 ± 8.69 [3.00]
Cerebrovascular disease	28	$38,280 ± $35,662 [$24,635]	9.30 ± 9.51 [8.00]	30	$30,138 ± $38,781 [$11,136]	4.90 ± 6.79 [2.00]
Overall (mean of 62 clinical classifications' mean values)	2,696	$31,349 ± $33,200 [$14,647]	8.76 ± 8.19 [6.00]	2,148	$25,136 ± $24,798 [$10,740]	6.04 ± 9.10 [3.00]

P-value <0.0001 for each comparison

Cost of Care

In most categories of clinical classifications, the cost of care for patients with constipation was greater than the cost of care for patients without constipation. The clinical classifications that demonstrated a significant difference between the costs of care in patients with versus without constipation were as follows: cerebrovascular disease, other connective tissue disorders, other gastrointestinal disorders, other injuries and/or conditions due to external causes, nontraumatic joint disorders, spondylosis, intervertebral disc disorders or other back conditions, fractures, and diseases of the heart. See Table 2.

As illustrated in Figure 1, the overall mean cost of care was greater in patients with constipation among many of the studied clinical classifications. Of the 62 total clinical classifications with a population of patients with and without constipation, 46 of these clinical classifications were associated with a higher mean cost of care for patients with constipation than for those without. Although the magnitude of the difference in cost of care between patients with and without constipation varied, the results showed a clear pattern where cost of care generally increased in the presence of constipation.

Length of Stay

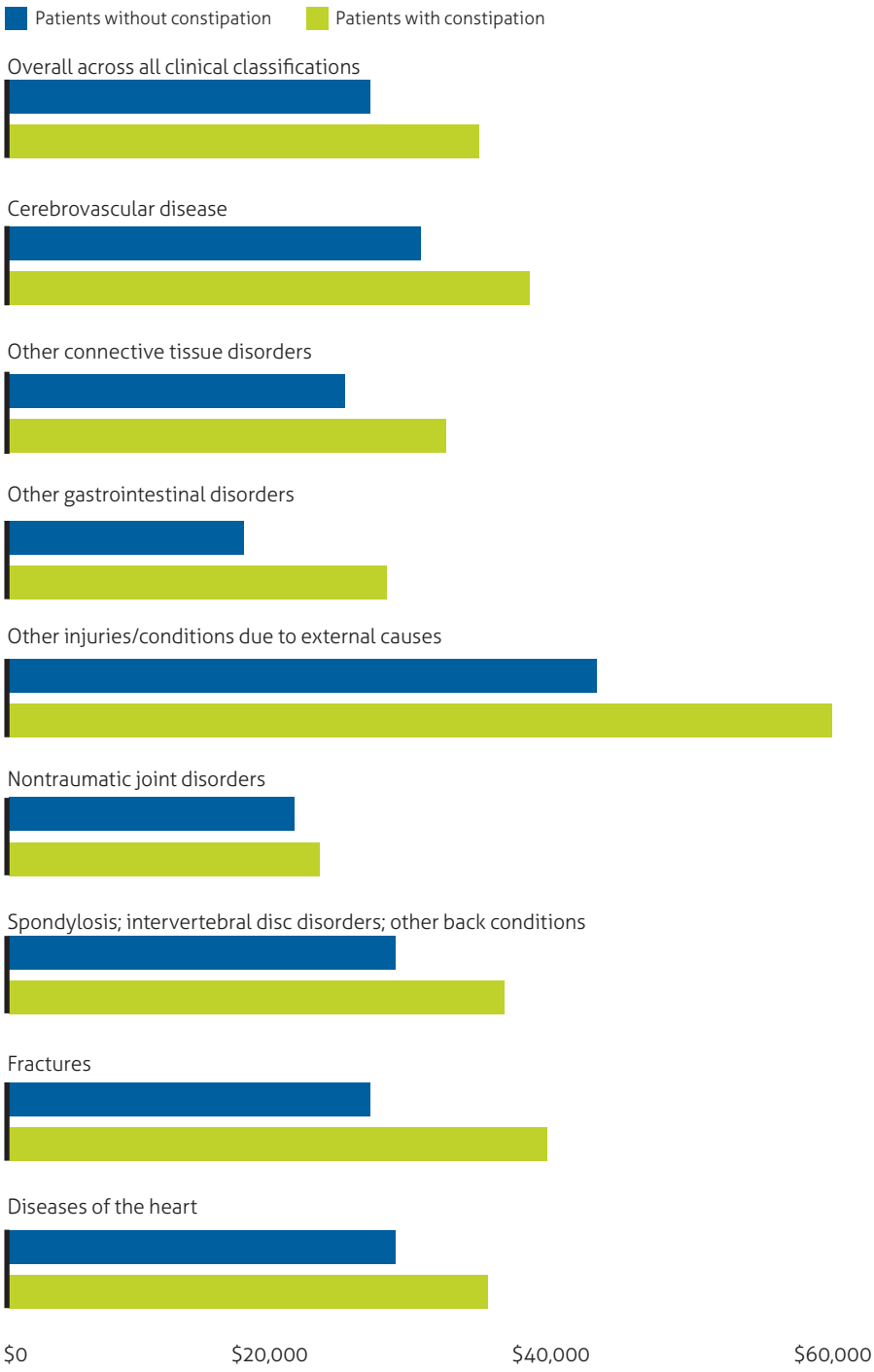
The results showed that patients with constipation generally had longer mean LOS than patients without constipation (Table 2). Some of the clinical classifications that showed the greatest difference in LOS between patients with and without constipation were as follows: cerebrovascular disease, other connective tissue disorders, other gastrointestinal disorders, other injuries and/or conditions due to external causes, nontraumatic joint

disorders, spondylosis, intervertebral disc disorders or other back conditions, fractures, and diseases of the heart. See Table 2. Based on the study results, longer LOS correlated with an increased cost of care.

The clinical classification that showed the greatest difference in LOS was cerebrovascular disease, with a mean difference between patients with and without constipation of 4.4 days (9.3 days and 4.9 days, respectively; P<0.001). There were notable differences in LOS between patients with and without constipation for various patient groups. Patients with fractures who experienced constipation had an increased LOS of 3.86 days compared to patients without constipation (9.38 days and 5.52 days, respectively). For patients with constipation and a diagnosis of other connective tissue disorders, the LOS was 3.68 days longer than that of patients without constipation (8.14 days and 4.46 days, respectively). Patients with constipation and other injuries and/or conditions due to external causes had an increased LOS of 3.41 days compared to patients without constipation (12.50 days and 9.09 days, respectively). For patients with constipation and other gastrointestinal disorders, the LOS was 2.72 days longer than that of patients without constipation (8.67 days and 5.95 days, respectively). Lastly, patients with constipation and diseases of the heart had an increased LOS of 2.7 days compared to patients without constipation (8.05 days and 5.35 days, respectively; P<0.0001, for all aforementioned differences).

As shown in Figure 2, these results support the finding that constipation in patients treated with opioids is commonly associated with a lengthening of the duration of inpatient hospitalizations. Overall, 54 of the total 62 clinical classifications demonstrated higher mean LOS for patients with constipation when compared to those without constipation.

FIGURE 1. COST OF CARE BY CLINICAL CLASSIFICATION



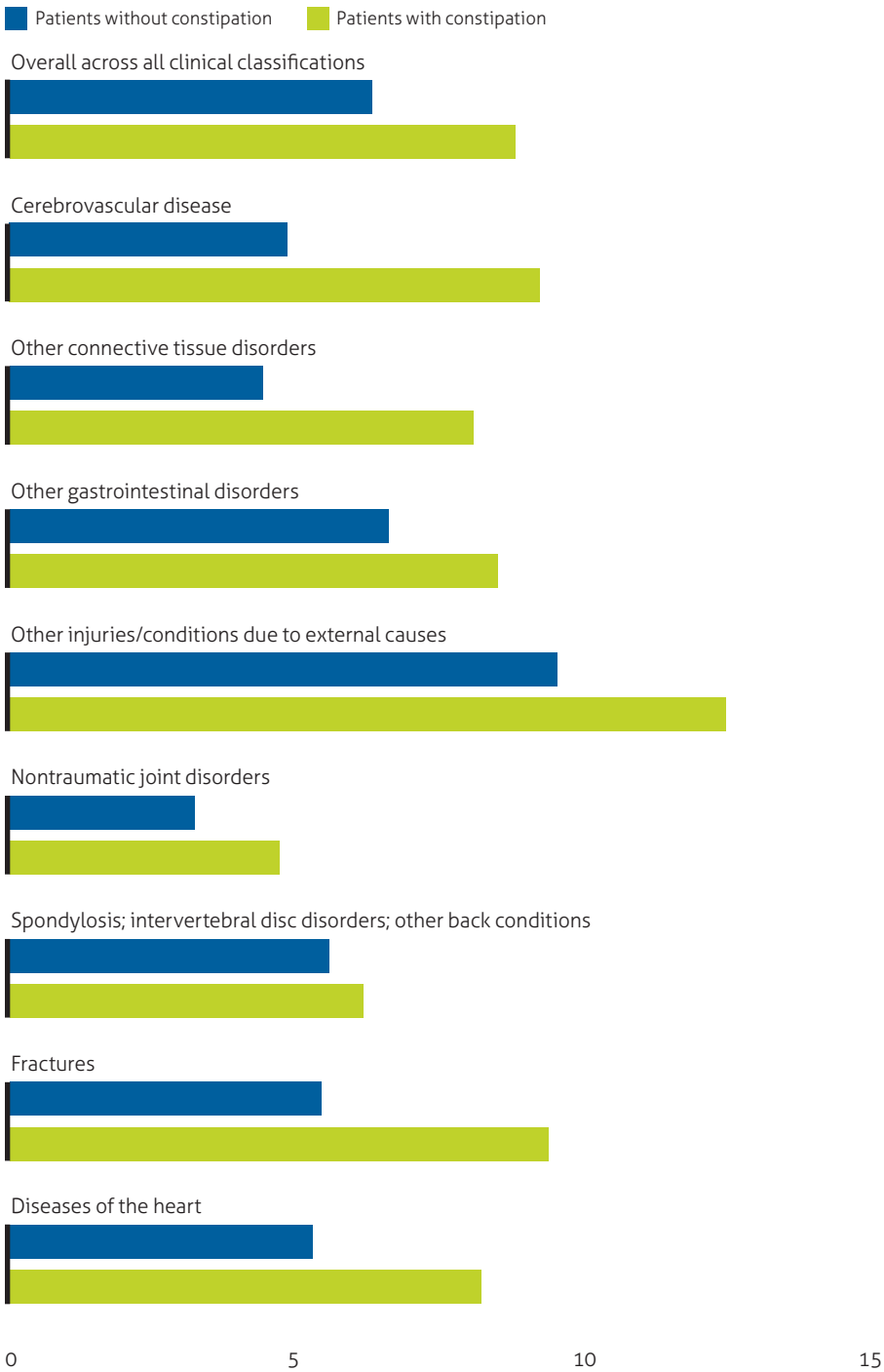
Discussion

For many diagnoses, costs and resource utilization were significantly increased overall for patients who received opioid therapy and experienced constipation. In addition to cost of care, average LOS was shown to be longer for patients with constipation than for those without constipation.

Prior studies that evaluated the cost and burden of constipation in ambulatory populations have shown similar results. Although not specific to the inpatient population, a 2009 survey in the Journal of Opioid Management evaluated the impact of OIC on patients with chronic non-cancer pain.[9]

The survey illustrated that participants who reported symptoms of OIC had more doctor visits (mean difference 3.84 visits; P<0.05) and more visits to an alternative care provider (mean difference 1.73; P<0.05) over the previous six months compared to patients without OIC.[9] In addition, participants with OIC reported greater time missed from work, impairment while working, and overall work impairment when compared with those without OIC.[9] A 2015 study published in American Health & Drug Benefits found that patients with OIC had greater mean inpatient LOS than patients without OIC.[3] The results of these two studies parallel the findings of this study, which suggests that OIC is associated with greater healthcare resource utilization and a larger economic burden.

FIGURE 2. LENGTH OF STAY (IN DAYS) BY CLINICAL CLASSIFICATION



In the present study, after further examination of the data accounting for variation in provider reimbursement rates, it was determined that the majority of the difference in the cost between the patients with and without constipation was due to complexity of the patient, as estimated by billed evaluation and management procedure codes (Appendix A). The inpatient coding strategies used categorizes the level of complexity for each patient, taking into account responsiveness to treatment, complications, and level of medical decision-making. Further analysis showed that more complex patients received a higher opioid dose and had a higher incidence of constipation. The treatment and prevention of constipation did not vary by patient complexity. The inconsistency between the escalating opioid dose and lack of corresponding adjustment in constipation prevention and treatment may negatively impact quality of life for these patients. Evidence shows that up to 85-95% of patients suffering from constipation related to opioid therapy report a degree of negative impact on quality of life.[6] Other factors that may impact patients' quality of life include other side effects, such as nausea, vomiting, and gastroesophageal reflux. These may contribute to increased LOS and cost for these patients.[5,7,9] The present study indicates that a treatment tailored to the complexity of each patient's clinical condition, while considering their clinical responses to previous therapies, may be beneficial for hospitalized patients of higher complexity who are using opioid products and who appear to be inadequately

managed by current treatment protocols.[10] The effective treatment of OIC may also improve pain management and increase quality of life for these patients.[10]

It should be noted that this study considered only inpatient billing and medication administration EMRs. The results of this study indicate that further study of the overall patient journey is warranted; however, to do so was cost- and time-prohibitive in this initial exploratory analysis.

Conclusion

Prior to this retrospective analysis, few studies examined OIC in hospitalized patients. The results and analysis from this study help to clarify the importance and significance of OIC treatment in the inpatient setting. The financial burden of OIC, especially in the hospitalized patient population, can be substantial, and addressing this issue is becoming increasingly important.[3] This research suggests that the observed increases in hospital costs and LOS for patients on opioid therapies who suffer from constipation may warrant efficacious management of constipation in this population and may yield positive impact on patients' health. Addressing constipation in patients receiving opioid treatment for pain management in an inpatient hospital setting, as well as providing treatment tailored to the complexity of individual patients, may result in increased quality of care for hospitalized patients as well as overall cost savings and shorter LOS.

APPENDIX A

Hospital Admission	
99221	Detailed or comprehensive history and exam Straightforward or low level medical decision-making
99222	Comprehensive history and exam Moderate level medical decision- making
99223	Comprehensive history and exam High level medical decision-making
Critical Care	
99291	Critical care, evaluation and management of the critically ill or critically injured patient; first 30-74 minutes
99292	Critical care, evaluation and management of the critically ill or critically injured patient; each additional 30 minutes
Subsequent Hospital Visits	
99231	Problem-focused interval history and problem-focused examination S or L medical decision-making Usually patient is stable, recovering, or improving
99232	Expanded problem-focused interval history and expanded problem-focused examination Moderate complexity medical decision-making Usually patient is responding inadequately to therapy or has developed a minor complication
99233	Detailed interval history and detailed examination High complexity medical decision-making Usually patient is unstable or has developed a significant complication or a significant new problem

Inpatient coding strategies provided by the American College of Physicians: See http://www.acponline.org/system/files/documents/about_acp/chapters/va/13mtg/johnson_codingtipstricks.pptx

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Osteoporosis in the Managed Care Setting:

A Rising Challenge with Growing Treatment Opportunities

Characterized as a systemic disorder resulting in structural deterioration of bone tissue and eventual depletion of bone mass, osteoporosis is an ongoing medical concern in the U.S., particularly because of the growing number of older women and men in the U.S.[1] The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) value at least 2.5 standard deviations below the average value in healthy subjects, known as a patient's T-score.[2] With lower T-scores, the likelihood of fracture rises, the most common sites of which include the vertebrae, proximal femur, and distal radius.[3]

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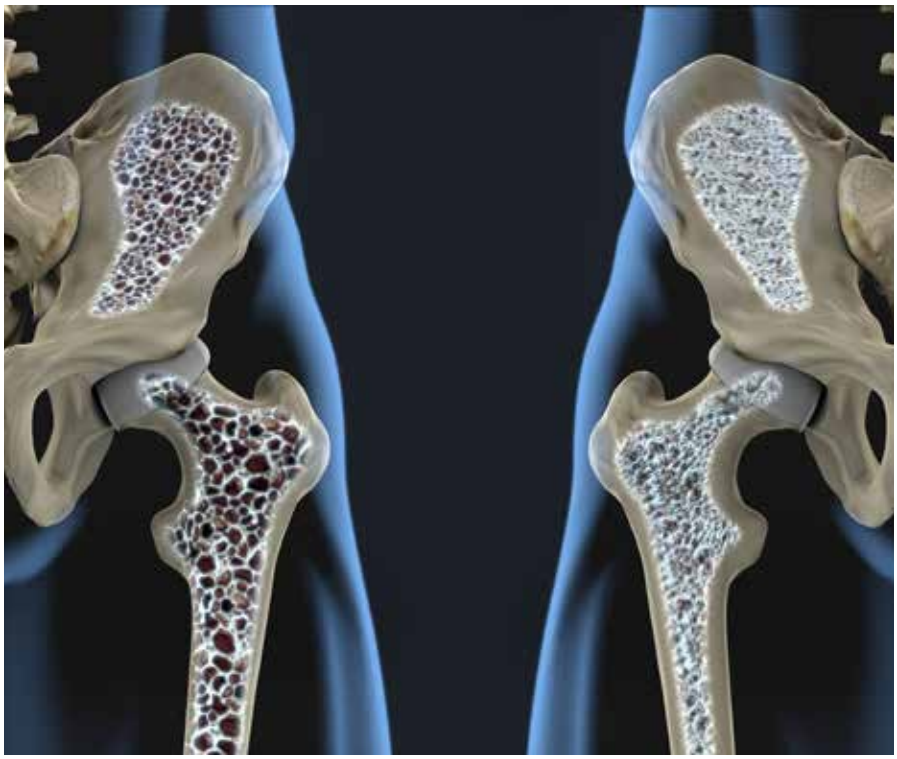
In recent years, a growing knowledge of bone pathophysiology has led to better use of available therapies as well as development of novel therapies and combinations with new mechanisms, which have improved standards of care in this area.

Incidence/Prevalence

Osteoporosis affects roughly 30% of all postmenopausal women in the U.S. and Europe.[3] Currently, it is estimated that more than 200 million people worldwide suffer from this disease. There are upward of 9 million osteoporotic fractures annually, with data suggesting that almost one in two women and one in five men will experience a fracture after age 50.[4,5] Due to its prevalence worldwide, osteoporosis is considered a serious public health concern. Notably, initial fracture is a major risk factor for a new fracture. Indeed, an increased risk of 86% for any fracture has been demonstrated in people who have already sustained a fracture.[4] National Health and Nutrition Examination Survey (NHANES) data noted an overall 10.3% prevalence of osteoporosis, with 10.2 million older adults with osteoporosis in the U.S.[6] Moreover, the overall low bone mass prevalence is 43.9%. Broken down by subgroup, 7.7 million non-Hispanic white, 500,000 non-Hispanic black, and 600,000 Mexican American adults have osteoporosis, with another 33.8 million, 2.9 million, and 2 million with low bone mass, respectively.[6]

Economic/Societal Burden of Osteoporosis

As the U.S. population ages, the rates of osteoporosis and resulting fractures will increase, with postmenopausal women incurring the majority of these fractures.[7] As a result, early diagnosis and effective treatment are extremely important. All major or proximal fractures and even minor fractures in some cases are associated with premature mortality, most notably in the first five years post-fracture.[8] Despite improvements in overall health and population mortality, post-fracture mortality has not changed in the last two decades, underscoring a need for early intervention.[8]



In addition to increased mortality, osteoporosis-related fractures often lead to lower quality of life and disability.[9] The estimated cost of osteoporosis and related fractures was $17 billion in 2005, though annual direct costs are expected to balloon to more than $25 billion by 2025, coinciding with the growing elderly population.[9,10] Costs differ by fracture type, with hip fracture accounting for 72% of all costs, and vertebral (6%), pelvic (5%), wrist (3%), and other types (14%) making up the rest.[10] Estimated individual costs are $16,663 for patients with hip fractures, $14,049 for patients with vertebral fractures, and $7,582 for patients with other types of fracture. Overall, osteoporosis-related fractures are associated with nearly $10,000 in additional direct costs per patient across all fracture types during the six months following fracture.[11]

Pathophysiology

Physiologically, a bone needs to be both stiff and flexible to resist fracture, which occurs when the force applied to a bone exceeds its strength. In human bone, collagen type 1 fibrils are wound in a triple helical structure and are linked together with non-collagenous proteins. This cross-linkage is reduced in osteoporotic bone, leading to reduced tensile strength.[5]

On a cellular level, osteoblasts, osteocytes, and osteoclasts are the three main types of bone cells. Osteoblasts (bone-forming) may become embedded within bone mineral as mature osteocytes (comprising 90-95% of the cells within bone) or remain on the surface as bone-lining cells. Osteoclasts (bone resorption) work with osteoblasts at specific sites on the bone surface to lay down new matrix for bone growth and repair. Osteocytes are critical for modeling, which occurs through adaptation to mechanical loading, and remodeling, which involves a cycle of resorption and reformation of existing bone.[5]

The fine balance between bone formation and resorption changes across the lifespan, with a positive balance during childhood until peak bone mass in early adulthood.[12] There is a subsequent period of stability followed by a negative balance in older age with higher osteoclast activity than osteoblast activity, leading to bone loss. Bone size, structure, and cellular activity differ between men and women, and bone loss is particularly accelerated after menopause in women.[5,13,14]

Clinical Risk Factors/ Diagnosis

Several factors increase the risk for fracture, including the following:[15]

- Higher age
- Glucocorticoid therapy
- Personal history of fracture
- Family history of hip fracture
- Current smoking
- Alcohol abuse
- Certain diseases

The risk factors above have been included in the FRAX® tool, a WHO-supported initiative that uses risk factors, with or without BMD measurement, to predict 10-year risk of fracture.[5,15] In terms of diagnosis, dual-energy X-ray absorptiometry (DEXA) is the standard for the evaluation of BMD and can be used to measure BMD at the hip, femoral neck, vertebrae, or wrist. As mentioned above, DEXA provides the patient's T-score, which is a standard deviation-based value using young, healthy control subjects at the peak of their BMD.[3] A T-score of ≤-2.5 indicates osteoporosis. DEXA scanning is recommended in all women over 65 years of age or in women aged 50 to 64 years with certain risk factors. Treatment is recommended with a T-score ≤-2.5, if there is a history of fragility fracture, or in the setting of osteopenia (T-score between -1.0 and -2.5) plus high risk for fracture.[7]

AVAILABLE TREATMENTS AND GUIDELINES

Traditional Therapy: Vitamin D and Calcium Supplementation

In recent years, there has been significant debate surrounding calcium and vitamin D supplementation in many fields of medicine.[3] For example, a large randomized controlled trial showed that supplementation

with vitamin D, calcium, or both for secondary fracture prevention appeared ineffective, while supplementation in high-risk settings (e.g. nursing homes) may be beneficial.[16,17] An issue that arose nearly a decade ago surrounded the association between excess calcium intake and increased cardiovascular risk, though this link has not been widely reproduced in other studies.[18] A recent meta-analysis of anti-fracture studies suggests that calcium and vitamin D supplementation in combination is associated with an improvement in mortality, which was not shown with vitamin D alone.[19]

Randomized controlled trials have also used varying calcium and vitamin D doses (e.g. 500-1,000 mg/day calcium; 250-1,200 IU/day vitamin D), and it has consequently been a challenge to establish standardized efficacy results. Nevertheless, it is generally recommended that patients consume enough calcium and vitamin D in their diet, as supplementation alone is less effective compared to pharmacological treatments discussed below.[3,20,21] Nearly all data evaluating the efficacy of anti-osteoporosis agents come from patients who were prescribed calcium and vitamin D together. As a result, they should be administered concomitantly in the setting of osteoporosis.[5]

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Pharmacotherapy: Mechanisms, Benefits, and Drawbacks

Bisphosphonates

From a pharmacotherapeutic standpoint, the majority of primary and secondary osteoporosis treatment involves bisphosphonate therapy. These agents inhibit bone resorption, resulting in increased BMD. This occurs through inhibition of farnesyl pyrophosphate synthase in the mevalonate pathway, which results in osteoclast apoptosis. Currently available bisphosphonates include alendronate (Fosamax®), ibandronate (Boniva®), risedronate (Actonel®, Atelvia®), and zoledronate (Reclast®, Zometa®).[3]

Bisphosphonates must be taken on an empty stomach due to interference of gastrointestinal absorption with food and liquids.[3] If taken as directed (in the morning with water, at least 30 minutes before food, drink, or other medications and remaining upright for 30-60 minutes), upper gastrointestinal side effects are less likely to occur.[5] If oral agents are not tolerated, intravenous zoledronate 5 mg can be delivered yearly for three years.[22]

Osteonecrosis of the jaw is a concerning side effect, though it has been limited mostly to patients with cancer who were receiving higher doses of bisphosphonates. The risk is lower for patients with osteoporosis who receive lower doses.[23] Atypical fracture is a potential complication of prolonged bisphosphonate use, warranting patient reassessment after three to five years.[3] Suboptimal administration can result in esophageal irritation, and poor adherence is associated with increased fracture rates.[24] There are also data suggesting that osteoclast inhibition can continue following bisphosphonate cessation, with markers of bone turnover 50% lower five years after discontinuation.[3]

Denosumab

Denosumab (Prolia®, XGEVA®; Amgen) is a fully human receptor activator of nuclear factor kappaB ligand (RANKL) antibody. Mechanistically, osteoclast precursors express RANK, which is activated by RANKL. RANK activation promotes the maturation of pre-osteoclasts into osteoclasts. Denosumab stops this maturation by binding to and inhibiting RANKL, which ends up decreasing bone resorption and increasing BMD.[3]

Three-year fracture data have demonstrated a 68% reduction in vertebral fracture and 40% reduction in hip fracture.[25] Denosumab is administered via subcutaneous injection every six months; and while side effects are uncommon, they include transient hypocalcemia (most prevalent in vitamin D deficient patients or in renal insufficiency) and cellulitis, which is thought to be secondary to an immunomodulatory effect of the agent.[3,5]

Raloxifene

Raloxifene (Evista®; Eli Lilly and Company) is a selective estrogen receptor modulator that acts as a partial estrogen agonist in bone, but an antagonist in other areas of the body such as the uterus and breast.[3] Consequently, its use has also been associated with a significant decrease in the risk of breast cancer.[5] Raloxifene has demonstrated the ability to slow deteriorating BMD and vertebral fractures in postmenopausal women.[26] While it has been shown to be effective in preventing postmenopausal bone loss and vertebral fractures, there has been no evidence that it prevents hip or non-vertebral fractures.

Adverse effects of raloxifene include leg edema, cramps, hot flashes, and a two- to threefold elevation in venous thromboembolism (VTE) risk.[5] For this reason, patients should be fully assessed prior to commencing treatment, and an active or past history of VTE (deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis) is a contraindication to administration.[3]

Teriparatide and Abaloparatide

Teriparatide (FORTEO®; Eli Lilly and

Company) is a recombinant form of parathyroid hormone (1-34).[3] In the osteoporotic patient, it increases renal reabsorption of calcium and increases intestinal calcium absorption via its effect on 25(OH)D3. For an anabolic effect, it is administered daily as a low-dose 20 µg subcutaneous injection for a period of 18 to 24 months.[3] Teriparatide has been shown to increase bone formation and produce large increases in BMD, leading to a 70% reduction in the incidence of vertebral fractures over 18 months.[27] Side effects are uncommon, but may include nausea, dizziness, and headache. The product label carries a boxed warning for risk of osteosarcoma, and transient hypercalcemia and hypercalciuria may also occur.[5]

In early 2017, the Food and Drug Administration (FDA) approved abaloparatide (TYMLOS™; Radius Health Inc.), a second parathyroid hormone-related peptide for subcutaneous injection. It is indicated for postmenopausal women with osteoporosis at high risk for fracture due to a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have not responded to other available therapy.[28] The recommended dose of abaloparatide is 80 µg administered subcutaneously once daily into the periumbilical region of the abdomen. The most common adverse reactions include hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo, and the product also includes a boxed warning for osteosarcoma.

Combination Therapy

Recent research has looked at combination therapy, with most trials assessing anabolic therapy (teriparatide) plus antiresorptive therapy (a bisphosphonate or denosumab).[3] While there has been insufficient power to draw meaningful conclusions in fracture outcomes, some trials have been able to show a difference in BMD particularly at the hip. Indeed, a greater BMD at the hip compared to the spine has been a consistent finding.[29] One study in particular, the DATA extension study, evaluated two years of concomitant teriparatide and denosumab therapy and found greater increases in BMD compared to single-agent therapy with either medication alone, and more than has been reported with any current therapy.[30] While combination therapy is promising, confirmation of fracture rate reduction is a remaining need in clinical trials.[3]

Treatment Guidelines

Decisions on which patients to treat and for how long are not always straightforward. The most recent guidelines for managing low BMD and osteoporosis have outlined two "strong" recommendations for fracture prevention in osteoporosis:[31]

- Offer a bisphosphonate or denosumab to women with known osteoporosis.
- Do not prescribe postmenopausal estrogens or raloxifene to treat women with osteoporosis.

Other "weak" recommendations include:[31]

- Drug therapy should be given for five years; going beyond five years should be based on reassessment of risks and benefits.
- Bisphosphonate therapy should be offered to men with "clinically recognized" osteoporosis.
- Clinicians should not monitor BMD during the initial five-year treatment period; no data have proven that monitoring improves fracture outcomes.
- For older women (age >65) with osteopenia and at high fracture risk, decisions should balance benefits and harms, and be based upon patient preferences and fracture risk.

From a managed care perspective, there are several avenues of exploration to improve treatment outcomes in osteoporosis.

IMPLICATIONS FOR MANAGED CARE

From a managed care perspective, there are several avenues of exploration to improve treatment outcomes in osteoporosis.

Identifying At-Risk Patients

Identification and treatment of patients at high risk for fracture in the managed care setting has been given a low-priority status in favor of higher-profile diseases like diabetes and cardiovascular disease.[32] However, with a growing older population and increased spending on osteoporosis and related fractures, identifying at-risk patients is increasingly important. Since certain subpopulations (e.g. women ≥65, men ≥70, those with prior fractures, patients on long-term corticosteroids, etc.) are at a higher risk for fracture and consequently are high healthcare resource users, they warrant proactive intervention from managed healthcare organizations.[32]

Determining Who Should Be Tested

DEXA is the gold standard for osteoporosis screening due to its low cost and widespread availability. Guidelines recommend testing in the following populations:[32]

- Women ≥65 years of age and men ≥70 years of age without a prior fracture
- All patients with a prior fracture
- Individuals on long-term corticosteroids
- Postmenopausal women with other risk factors (e.g. low BMI, smoking, family history of osteoporosis).

Ensuring Patients with Osteoporosis Are Treated

Survey data have shown that more than one-third of patients did not initiate recommended osteoporosis medication despite confirmed diagnosis, with reasons including concern over side effects (77.3%), medication costs (34.1%), and preexisting gastrointestinal concerns (25.0%).[33] Another retrospective analysis showed even higher rates of non-treatment (64.3%) and that untreated patients with osteoporosis were slightly older and had higher rates of hypertension, chronic inflammatory joint disease, diabetes mellitus, and gastrointestinal events ($P \leq 0.01$) compared to treated patients.[34] These data suggest the need for increased scrutiny to ensure patients with osteoporosis are adequately treated in the managed care setting.

Engaging Patients in Treatment

Methods to increase patient engagement may include:

- Disease or case management programs that target higher-risk patients, with telephonic outreach to promote DEXA testing in appropriate patients
- Offering prescription coverage of over-the-counter calcium or vitamin D supplements for patients >65 or 70 years of age with low dietary intake
- Telephonic outreach to promote adherence[32]

Managed care organizations may also consider offering incentives to clinicians who promote the timely identification and treatment of individuals at risk for fracture. This could include incentives for higher rates of starting osteoporotic treatment in at-risk or diagnosed individuals.[32,35] Ultimately, the two-part goal of these programs is to (1) identify high-risk patients and (2) raise awareness of those higher-risk patients who remain undiagnosed and untreated.[32]

PIPELINE AGENTS/ FUTURE DIRECTIONS

Despite tremendous therapeutic advances in the last 15 to 20 years, there is an increasing treatment gap for patients at high fracture risk.[36] Notably, in recent years, the approach to developing novel therapeutics has changed from one driven by discoveries in animal studies and clinical observations (e.g. estrogen, teriparatide, calcitonin) or repurposing existing compounds (e.g. bisphosphonates) to one guided by enhanced understanding of bone biology (e.g. denosumab) coupled with the study of patients with rare bone diseases. Novel areas of study include anti-sclerostin antibodies, with promising results to date.[36]

Anti-Sclerostin Antibodies: Romosozumab and Blosozumab

Romosozumab (Amgen) is a humanized monoclonal antibody that prevents sclerostin from inhibiting osteoblast maturation and function.[3,37] More specifically, sclerostin blocks the Wnt signaling bone-formation pathway by permitting the engagement of Wnt ligands with their co-receptors, resulting in an increase in bone formation and BMD.[38] Early trial data evaluated the safety and tolerability of multiples doses of romosozumab and found that it was well-tolerated and associated with significant improvements in BMD of the lumbar spine in every dose cohort.[39] Data suggest that monthly subcutaneous dosing of romosozumab reduces the risk of vertebral and clinical fractures in women with postmenopausal osteoporosis.[38] Phase II data showed a significant mean change in lumbar BMD at 12 months (+11.3%) in the romosozumab 210 mg monthly dose compared with a decrease of 0.1% in the placebo group and increases of 4.1% with alendronate and 7.1% with teriparatide.[40] The overall incidence of adverse events was similar between groups, with the exception of the increased frequency of injection-site reactions in the romosozumab groups. More recently, data from phase III studies linked romosozumab to an increased risk of cardiovascular adverse events, prompting the FDA to reject the manufacturer's application for approval of the investigational agent.[41] In a press release, Amgen commented that it no longer anticipates receiving FDA approval in 2017, and the FDA confirmed the rejection of romosozumab in a complete response letter.[41] The FDA has requested that, for resubmission purposes, Amgen complete an application that contains data from the ARCH, FRAME, and BRIDGE trials.[41] Blosozumab (Eli Lilly and Company) is another anti-sclerostin antibody that is currently in phase II clinical trials.[3]

In osteoporosis, there has been recent difficulty in the development of new drugs, with the failure and/or withdrawal of several therapies including arzoxifene, lasofoxifene, MK-5442, roncalceret, and odanacatib.[42] Currently, romosozumab is the only novel agent presently in phase III development. However, ongoing research into the mechanisms and signaling pathways of bone remodeling and regulation will hopefully open new doors for drug development.[42]

CONCLUSIONS

In recent decades, our understanding of the pathogenesis of osteoporosis has increased significantly. With the release of several classes of medication in the past two decades, clinicians are afforded several avenues of treatment for this growing problem in our country. From a managed care standpoint, identifying at-risk patients, determining who should be tested, ensuring patients with diagnosed osteoporosis are treated, and engaging patients in their treatment regimens are some of the several critical factors that can help ensure treatment success.

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Star Ratings and Quality Improvement Programs:

New Measures and Program Successes

The Star Rating system is a scoring system that was created by the Centers for Medicare & Medicaid Services (CMS) to measure plan performance and quality for Medicare Advantage (MA) and Medicare Part D plans/prescription drug plans (PDPs).[1] Each year, CMS publishes the Part C and Part D Star Ratings, and reviews the measures that comprise the ratings.[1]

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CMS has identified 34 Part C measures, many of which are considered improvement measures. CMS, the National Committee for Quality Assurance (NCQA), and the Pharmacy Quality Alliance (PQA) are continuously evaluating Star measures, making enhancements to current measures, and generating new measures as well. Notable Part C improvement measures (which are also Healthcare Effectiveness Data and Information Set [HEDIS] measures) that have related Part D measures and/or are likely to involve prescription drug use or require a medication review include the following:[2]

- Care for older adults – medication review
- Diabetes care – eye exam
- Diabetes care – kidney disease monitoring
- Diabetes care – blood sugar controlled
- Controlling blood pressure
- Osteoporosis management in women who had a fracture
- Rheumatoid arthritis (RA) management

CMS has also identified 14 Part D measures, and the pharmacy-related measures include:[2]

- Medication adherence for diabetes medications
- Medication adherence for hypertension (renin-angiotensin system [RAS] antagonists)
- Medication adherence for cholesterol (statins)
- Medication therapy management (MTM) program completion rate for comprehensive medication review (CMR)

The pharmacy-related HEDIS Star measures include:[3]

- Statin use in patients with cardiovascular disease
- Statin use in persons with diabetes

Managed care pharmacists are uniquely positioned to assist plans in achieving these quality measures that are intended to improve the care of plan beneficiaries. Achieving these measures ultimately improves patient outcomes through better medication management. Pharmacists can perform a review of pharmacy and medical claims to determine whether beneficiaries are being prescribed and are adherent to pharmacological therapies and undergoing the appropriate testing and monitoring for the maintenance of their conditions. Achieving these goals is also beneficial to payors because plans achieving 4- and 5-star status are eligible to receive 5% quality bonus

payments (QBPs).[4,5] Plans with 5-star status can enroll members year-round, whereas plans with a lower star status can only enroll members during the annual enrollment period.[6] This represents an opportunity for plans to generate additional revenue. Studies have supported the notion that higher Star Ratings may increase the likelihood that members will enroll in these higher-rated plans.[7]

Furthermore, each 1-star overall improvement from 3- to 4-star status is worth an estimated $50 per member per month.[8] Better medication adherence to RAS antagonists and statins by Medicare beneficiaries with diabetes (two Star Ratings targets) have demonstrated reductions in unnecessary medical spending (e.g. hospitalizations, readmissions, etc.).[9]

CMS reserves the right to terminate contracts for MA plan sponsors that fail to achieve at least 3-star status for at least one out of three consecutive years.[10] To improve their scores, many plans have implemented quality improvement programs that are designed to increase the number of beneficiaries who are adherent to their diabetes, hypertension, and cholesterol medications, and who undergo appropriate testing and monitoring for their conditions. These programs involve offering beneficiaries preventive care and helping members better manage their chronic conditions.[4] Outreach efforts typically consist of patient-specific discussions focusing on gaps in care, barrier assessments and analysis, academic detailing and clinical decision support, patient- and provider-tailored communication, and follow-up. Outreach methodologies may involve clinical pharmacist/administrator outreach to providers via phone calls, interactive voice response calls, texts, emails, faxes, or mailings and, when appropriate, member and/or pharmacy outreach to discuss the program and share the results of provider discussion.

CMS reserves the right to terminate contracts for MA plan sponsors that fail to achieve at least 3-star status for at least one out of three consecutive years.

Analytics may involve the review of pharmacy and medical claims data and enrollment information. It can be very powerful to review both medical and pharmacy data to identify all the opportunities and/or gaps that each member has and then address them in a single conversation. Databases should be equipped to track outreach logs and encounters, call center metrics and reporting, and workflow/process management. Plans seeking to implement quality improvement programs should be prepared to proactively identify and leverage opportunities that impact multiple quality measures. For example, plans should aim to achieve the Part C measure of diabetes care – blood sugar controlled by also seeking to achieve the Part D measure of medication adherence for diabetes medications. Plans should also retain pharmacist services for MTM, which can include CMR completion or targeted medication review. Pharmacy technicians and nurses may also be able to assist with other outreach efforts including addressing patient concerns, identifying other services that may be beneficial to the patient, and facilitating care coordination efforts. These efforts may be linked to increasing member satisfaction as measured through the Consumer Assessment of Healthcare Providers & Systems survey. Finding information from the plan, in addition to the overall rating of the health plan and rating of the drug plan, are all Star Ratings measures that could be impacted by this activity as well.

Magellan Rx Management delivers customized clinical programs that drive Star Ratings improvements. Examples of such programs include the former Star Diabetes Treatment Program (previous measure) and the Star RA Management Program. The Star Diabetes Treatment Program included intensive pharmacist outreach to physicians, patients, and pharmacies to improve appropriate medication therapy and drive desirable behaviors. The various methods of member engagement and clinical intervention included sending member letters, performing telephonic outreach to members, sending outreach materials to prescriber offices and community pharmacies, and scheduling evening calls to reach members with busier schedules. This program, executed on behalf of an MA client, resulted in a 2-star im-

Magellan Rx Management delivers customized clinical programs that drive Star Ratings improvements. Examples of such programs include the former Star Diabetes Treatment Program (previous measure) and the Star RA Management Program.

provement from 1- to 3-star status. The Star RA Management Program included intensive pharmacist outreach to physicians, patients, and pharmacies to improve appropriate medication therapy, correct erroneous billing practices, and drive desirable behaviors. This program, also executed on behalf of an MA client, resulted in a 1-star improvement from 3- to 4-star status in one year of the program followed by a jump to 5-star status in year two. Both programs improved medication use without sacrificing quality of care for plan beneficiaries.

In an announcement this spring to MA organizations, PDP sponsors, and other interested parties, CMS included information regarding forecasted measures for 2019 Star Ratings.[11] Notable pharmacy-related potential changes to existing measures and potential new measures for 2019 and beyond include CMS Innovation Model Tests and opioid overuse (Part C), respectively.[11]

In an announcement this spring to MA organizations, PDP sponsors, and other interested parties, CMS included information regarding forecasted measures for 2019 Star Ratings.

The potential CMS Innovation Model Test refers to the MA Value-Based Insurance Design model involving the Part D Enhanced MTM model.[11] With this model, CMS seeks to test if additional payment incentives and regulatory flexibilities for Part D sponsors produce MTM program enhancements and reductions in net Medicare spending.[11] MTM program CMR completion rates would be calculated using available plan-reported data from the plans under the Part D contract.[11]

The potential new opioid overuse measure would entail two additional measures of opioid overuse beyond the three PQA opioid measures approved by NCQA.[11] The two additional measures under consideration are the use of multiple prescribers and multiple pharmacies.[11] Multiple prescribers would be measured by the percentage of members receiving prescriptions for opioids from ≥4 prescribers during the measurement year; and multiple pharmacies would be measured by the percentage of members receiving prescriptions for opioids from ≥4 pharmacies during the measurement year.[11]

Star Ratings should be a focus for MA and PDP plan sponsors, as higher Star Ratings are necessary to remain competitive in the market, increase enrollment and the likelihood of QBP receipt, and reduce unnecessary medical costs. Most importantly, strong performance on these measures ensures members are optimizing medication use, which can lead to better outcomes. Plan sponsors are encouraged to remain up-to-date regarding changes to Star Ratings for the coming year, especially for the potential changes to the existing measures and new measures that may be used.

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Variable Fee Schedule Reimbursement:

Impact on Antiemetic Utilization and Quality of Care

Based on current fee-for-service (FFS) payment models, reimbursement for intravenous (IV) 5-HT3 receptor antagonists (5-HT3-i's), administered for the prevention of chemotherapy-induced nausea and vomiting (CINV), may be driven by drug acquisition cost and can vary greatly across all available products.

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Presently, there are considerable cost differences among the various 5-HT3-i's. In an effort to control the high costs associated with these treatments, payors have employed a variety of management strategies, including formulary restrictions, step therapy requirements that mandate the use of less costly alternatives, prior authorizations, and competitive acquisition practices.

Treatment guidelines and best practices for the use of antiemetics for CINV have most often been driven by both clinical evidence and cost considerations.[1,2] Treatment guidelines for the use of IV antiemetics, including IV 5-HT3-i's, are published by the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology.[3]

Of note, both the ASCO and NCCN guidelines have noted that IV palonosetron is the preferred 5-HT3-i following moderately emetogenic chemotherapy (MEC).[4,5] In addition, the Quality Oncology Practice Initiative (QOPI) 2016 Qualified Clinical Data Registry (QCDR) measures, which were updated to reflect the ASCO Clinical Practice Guidelines Update, are consistent with the 2015 QCDR measures regarding the following patient population: the percentage of adult patients with a cancer diagnosis who receive MEC or highly emetogenic chemotherapy (HEC), respectively, and are prescribed palonosetron or a first-generation 5-HT3-i and dexamethasone or palonosetron or a first-generation 5-HT3-i and dexamethasone and aprepitant/fosaprepitant, respectively.[5,6]

Within the MEC category there is variation in terms of emetogenicity among the chemotherapy agents; ASCO and NCCN consider any agent with a frequency of expected emesis between 30-90% to be MEC. The MEC list also does not differentiate chemotherapy that has high delayed emesis potential. In the studies that showed palonosetron is superior to ondansetron and granisetron, doxorubicin and cyclophosphamide were considered MEC at lower doses. These agents have higher potential for delayed emesis and are considered HEC at higher doses. Many of the phase III studies showed palonosetron was not superior to the other 5-HT3-i's for acute nausea and vomiting but was superior for delayed nausea and vomiting. NCCN and ASCO separated some chemotherapy agents to either the HEC or MEC category based on dosage. For

Treatment guidelines and best practices for the use of antiemetics for CINV have most often been driven by both clinical evidence and cost considerations.

example, ifosfamide >2g/m^2 was considered HEC, but <2g/m^2 was considered MEC. Palonosetron can be used for some MEC drugs (e.g. carmustine, cyclophosphamide, doxorubicin, epirubicin, and ifosfamide) that have delayed emesis potential, regardless of dose.

Due to its high cost, the fairly broad category of CINV treatments for MEC, and the current FFS reimbursement model, many payors have employed a variety of the aforementioned management strategies to restrict inappropriate access to palonosetron. The use of palonosetron in the settings of low emetogenic chemotherapy (LEC) and minimally emetogenic chemotherapy (MinEC) represent inappropriate, high-cost use.

A retrospective study was conducted to evaluate the impact of a variable fee schedule reimbursement (VFSR) model — which increases physician reimbursement for all physician office-administered 5-HT3-i's to match that of the most expensive product, regardless of drug acquisition cost — on 5-HT3-i utilization and guideline-recommended 5-HT3-i use in adult patients receiving MEC or HEC. Standardizing 5-HT3-i reimbursement has the potential to minimize payor restrictions on treatment choice and ultimately allow physician autonomy and patient-centered decision-making during the drug selection process without concern of financial bias. It is for this reason that some payors have already elected to transition from the original FFS payment model to a VFSR model.[7]

Methodology of the Retrospective Study

A retrospective medical claims study was performed using data from a health plan with approximately 2.3 million commercial lives. Patients included in the study were those with a cancer diagnosis and a claim for physician office-administered 5-HT3-i's during the baseline period and the intervention period. Utilization of all 5-HT3-i's, including dolasetron, granisetron, ondansetron, and palonosetron, was analyzed on a quarterly basis. Data for each 5-HT3-i was evaluated to determine total claim count, unique members, and plan paid cost. In addition, the average market share for branded IV palonosetron was evaluated in quarterly increments prior to July 2009, when the VFSR model was implemented, and after July 2009. Furthermore, claims were analyzed to assess whether they met the aforementioned QOPI 2016 QCDR measures for patients who have received either MEC or HEC. Utilizing the QOPI 2016 QCDR moderate-risk measure, the number of patients with a claim for MEC or HEC within zero to three days of a claim for palonosetron or a first-generation 5-HT3-i was also measured, as the study criteria defined inappropriate use as patients with a cancer diagnosis (as determined by ICD-9 or ICD-10 code) with a palonosetron claim without MEC or HEC within zero to three days of the claim.[2,6]

The moderate-risk measure was calculated using a numerator of the number of all patients who have received palonosetron with a service date of zero to three days prior to the service date of chemotherapy and a denominator of all members 18 years of age or older who have received MEC that was associated with an oncology ICD-9 or ICD-10 code. The high-risk measure was calculated using a numerator of the number of patients who have received any 5-HT3-i with a service date of zero to three days prior to the service date of chemotherapy and a denominator of all members 18 years of age or older who have received HEC that was associated with an oncology ICD-9 or ICD-10 code. For both measures, chi-square tests were performed to detect statistical significance between the baseline period and intervention period.

Results of VFSR Model Implementation

The analysis of 141,276 claims resulted in 16,875 claims for 2,289 members (7.37 claims per member) accounting for a total plan paid amount of $5,194,165 during the baseline period and 20,291 claims for 2,819 members (7.19 claims per member) with a total plan paid amount of $4,267,738 during the intervention period. During the baseline period, there were 1,171 claims for dolasetron (6.9%), 1,296 claims for granisetron (7.7%), 1,251 claims for ondansetron (7.4%), and 13,157 claims for palonosetron (78.0%) (combined N=16,875); whereas during the intervention period, there were 7 claims for dolasetron (0.04%), 1,833 claims for granisetron (10.0%), 7,289 claims for ondansetron (39.7%), and 9,210 claims for palonosetron (50.2%) (combined N=18,339). The total number of unique members with claims for dolasetron (245 vs. 4), granisetron (229 vs. 332), ondansetron (273 vs. 1,184), and palonosetron (1,985 vs. 1,794) differed between the baseline and intervention periods. (Note: This analysis does not consider the impact of external market influences, preferred drug list changes, or guideline updates that may have contributed to utilization pattern changes.)

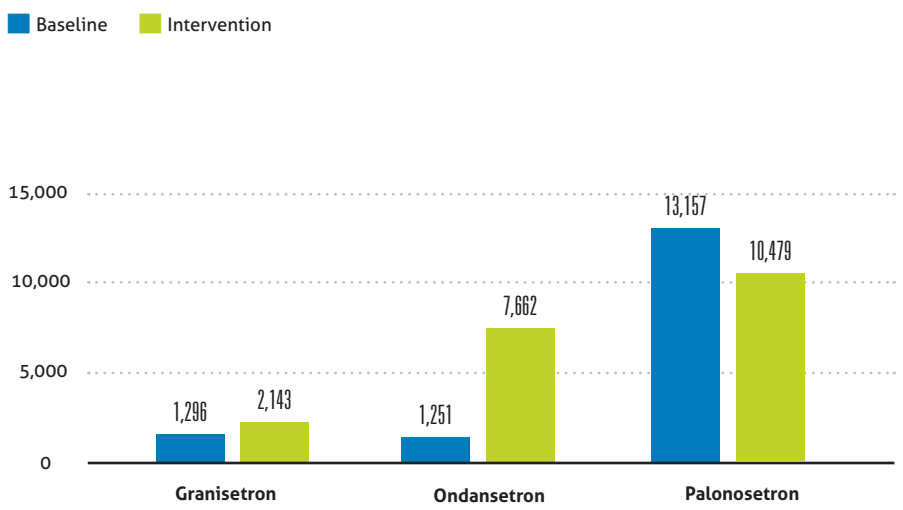
The total plan paid costs for dolasetron ($52,576 vs. $283), granisetron ($218,897 vs. $68,203), ondansetron ($140,198 vs. $50,470), and palonosetron ($4,782,494 vs. $4,148,783) differed between the baseline and intervention periods. Of note, prior to implementation of VFSR, palonosetron represented 78% of the market share for all 5-HT3-i claims; whereas after implementation of VFSR, palonosetron market share declined to 51.6% (P<0.0001).

Utilization of the generic 5-HT3-i's,

granisetron and ondansetron, increased between the baseline period and the intervention period (1,296 to 2,143 claims vs. 1,251 to 7,662 claims, respectively), whereas utilization of dolasetron and palonosetron decreased (1,171 to 7 claims vs. 13,157 to 10,479 claims, respectively) during these same time periods (Figure 1).

In addition, the total plan paid amount decreased consistently across all quarters throughout the year. In 2008, the total plan paid amount was $5,194,165 compared to $4,267,738 in 2015, which represents an estimated annual cost avoidance of $926,427. Note that these figures are not adjusted for inflation (Figure 2).

FIGURE 1: NUMBER OF CLAIMS PRE- AND POST-VFSR

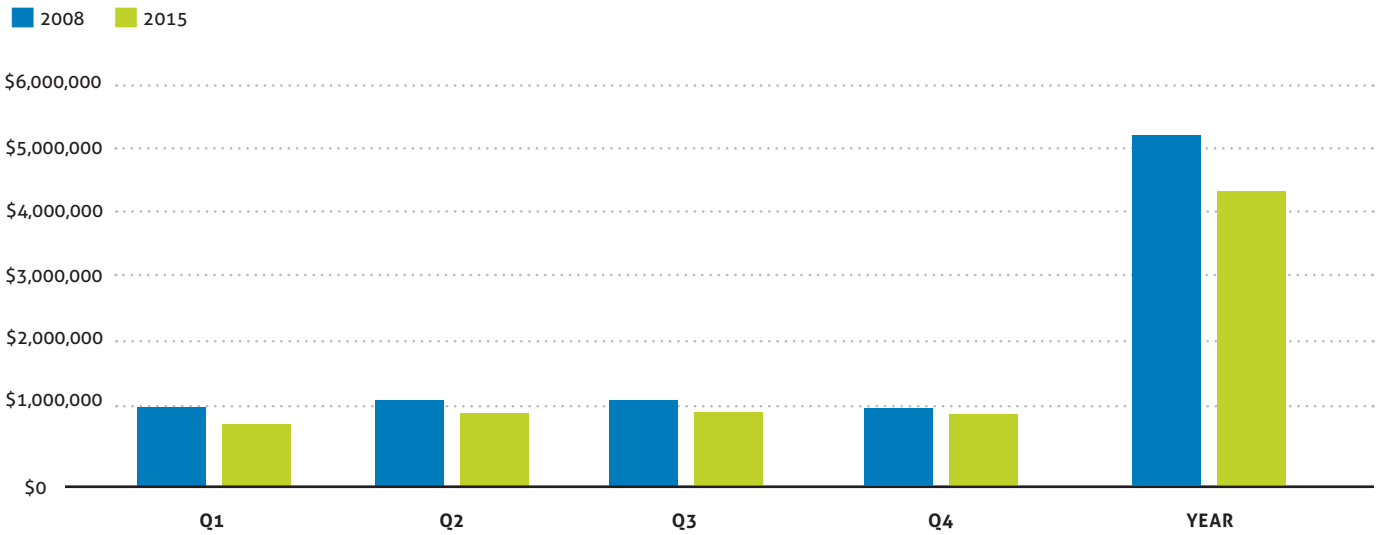


Implications for Managed Care

The QOPI 2016 QCDR measures include the use of palonosetron or another 5-HT3-i in both HEC and MEC. Patients receiving HEC and physician office-administered palonosetron or another 5-HT3-i decreased from 97.8% to 95.3%. Patients receiving MEC and physician office-administered palonosetron or another 5-HT3-i decreased from 97.2% to 94.1%. Both results were statistically significant. However, given that this study was conducted using medical claims data, additional pertinent information, such as treatment being declined by the patient, contraindications to treatment, or other clinical exclusions — all of which are considered denominator exclusions/exceptions by QOPI QCDR measures — is not available. Therefore, it is possible that patients who were identified for inclusion in this measure should not have been included in this portion of the analysis, thus affecting the measures being reported in these baseline and intervention periods.

Between the baseline and intervention periods, utilization of the generic 5-HT3-i's, granisetron and ondansetron, increased, whereas utilization of dolasetron and palonosetron decreased. The most notable shift in

FIGURE 2: TOTAL PLAN PAID AMOUNT PRE- AND POST-VFSR



utilization was observed for ondansetron claims, which resulted in substantial savings to payors. This utilization shift may lead to more cost-effective treatment without reducing quality of care. Furthermore, the 20.3% decline observed for palonosetron utilization was largely driven by the reduction in inappropriate use of palonosetron by 61.6% between the baseline and the intervention period. Of note, following VFSR implementation, appropriate use of 5-HT3-i's among patients receiving HEC remained unchanged. As mentioned previously, the use of palonosetron for LEC and MinEC represent inappropriate, high-cost use.

Our analysis suggests that VFSR implementation demonstrates a beneficial impact on utilization and inappropriate use of palonosetron without compromising quality of care among patients with cancer who are receiving treatment with MEC or HEC. In addition, this reimbursement model has the potential to generate cost savings without removing physician autonomy from the treatment selection decision-making process. The results of this study suggest that an opportunity exists for the implementation of VFSR to remove financial bias from the treatment selection process, while increasing the likelihood that patients will receive both clinically and cost-effective antiemetic care. It is recommended that additional studies be conducted and more robust claims data be accessed, potentially including electronic medical records and/or office notes, to confirm the results of this retrospective medical claims analysis.

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Contraceptive Clinical Outreach Program:

Addressing High Unintended Pregnancy Rates

In the U.S., the unintended pregnancy (UIP) rate has dropped from 54% in 2008 to 45% in 2011.[1] A UIP is one that is either mistimed or unwanted.[1] This all-time-low UIP rate is likely due to an overall increase in contraceptive use. However, despite the increase in contraceptive use and the wide variety of contraceptive devices and therapies available, nearly half of all pregnancies are still unintended. UIPs are largely due to not using birth control or incorrect or inconsistent use of contraceptive methods.[2]

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Long-acting reversible contraceptives (LARCs), including intrauterine devices (IUDs) and contraceptive implants, have been shown to be the most effective reversible contraceptive methods. The effectiveness of these contraceptive methods does not rely on patient adherence, resulting in a negligible failure rate.[3] Although various LARCs are available, only about 12% of contraceptive users reported using LARCs in 2012, with just over 10% of those using an IUD.[2] Of note, this rate does reflect an increase from 2.4% in 2002.[4]

Public Costs of Unintended Pregnancies

Among women whose income is below 100% of the poverty limit, pregnancy rates are higher among women who did not graduate high school compared to those who graduated high school, have completed some college/associate degree, or graduated from college.[5] Furthermore, the rate of UIPs is highest among women under 25 years of age compared to women outside of this age group.[6]

Approximately 51% of U.S. births are covered by Medicaid or other public insurance programs.[7] In 2010, public insurance program expenditures related to UIPs in 19 states exceeded $400 million.[8] Government expenditures on the births, abortions, and miscarriages resulting from UIPs nationwide totaled $21 billion in 2010; that amounts to 51% of the $40.8 billion spent for all publicly funded pregnancies that year.[8] In 2010, a publicly funded birth cost an average of $12,770, including prenatal care, labor and delivery, postpartum care, and 12 months of infant care.[8] This cost increases to $20,716 when 60 months of care are included.[8] It is estimated that by averting all UIPs in 2010, the total gross potential savings would have been about $15.5 billion.[8] Increasing accessibility and utilization of contraceptive therapies including LARCs may result in successful prevention of UIPs and, ultimately, cost savings.

Availability of and Barriers to LARC Utilization

While most short-acting hormonal methods of contraception are widely available with few barriers to utilization, many long-acting therapies have barriers to utilization that persist. The six LARCs available in the U.S. include five IUDs (ParaGard®, Skyla®, Mirena®, Kyleena™, and Liletta™) and one subdermal implant (Nexplanon®). Copper is the active ingredient in ParaGard®, which is believed to prevent conception by interfering with sperm transport and fertilization and perhaps preventing implantation. The other IUDs employ levonorgestrel, a synthetic hormone thought to provide contraception by thickening the cervical mucus, which inhibits sperm passage through the cervix, thereby precluding fertilization, inhibiting sperm mobility and function, and altering the endometrium. The active ingredient in the subdermal implant Nexplanon® is another synthetic hormone, etonogestrel, which is thought to prevent conception by suppressing ovulation, increasing the thickness of cervical mucus, and altering the endometrium.

The high up-front cost of LARCs, coupled with misconceptions or a lack of information about them, among providers and patients alike, contribute to the low rate of LARC utilization, despite the potential benefits and ease of use.[9] Medicaid reimburses for LARCs. According to the Guttmacher Institute 2014 report, for every dollar spent on contraceptive services, Medicaid saved $5.68 in cost associated with UIP and pregnancy care.[10] The Contraceptive CHOICE Project promoted the use of LARCs by removing financial and knowledge barriers; the results showed that once financial barriers were removed and patients received comprehensive counseling on LARC options, two-thirds of women in the study chose to utilize LARCs.[9]

LARC utilization has the potential to decrease UIPs, thus reducing the economic burden. With LARCs considered the most effective contraceptive options by many family-planning experts, LARC methods are regarded as essential in decreasing the rate of UIP.[7] Increasing access to highly effective LARC methods may result in a significant decrease in the rate of and the costs associated with UIPs in the U.S.

In an effort to target a population at high risk for UIP, Magellan developed and implemented a Contraception Educational Outreach Program designed to improve appropriate utilization of all contraceptive therapies, including LARCs, within Magellan Complete Care (MCC) of Florida.

Magellan Clinical Program

In an effort to target a population at high risk for UIP, Magellan developed and implemented a Contraception Educational Outreach Program designed to improve appropriate utilization of all contraceptive therapies, including LARCs, within Magellan Complete Care (MCC) of Florida, a Medicaid managed care plan. At a rate of 59%, the state of Florida has one of the highest UIP rates in the U.S.[11] This program was designed to effectively relay educational materials and information regarding all contraceptive therapies to an at-risk population in an effort to decrease rates of UIPs. By engaging directly with patients and facilitating proper communication with providers, this program sought to streamline the process of contraceptive education, evaluation, and, ultimately, utilization. The value of a contraception intervention program had become increasingly clear, with patient engagement as a top priority. Clinical programs designed to improve outcomes are meaningful to payors, but increasing contraception utilization to impact rates of UIP requires member engagement as rates of patients falling out of care tend to be high within Medicaid populations.

MCC covers 42,000 members, 16,834 of whom are of childbearing age, with approximately 500 pregnancies per month. Target identification criteria for the clinical program were females of childbearing age (or those 18 to 45 years old) with poor adherence to oral contraceptive therapy per claims-based data analysis and who had no claims for LARC. Magellan identified 1,500 healthcare providers (HCPs) as targets for this program.

The overall clinical pharmacist outreach strategy included three main components. First, initial provider outreach was conducted in order to educate the provider regarding the clinical program initiative, discuss patient-specific opportunities, and identify provider barriers to utilizing all contraceptive therapies, including LARCs. Next, clinical pharmacists performed initial member outreach, discussing current contraception therapy, educating members on all contraception types (including LARCs), and facilitating member follow-up with their provider for contraception evaluation, if appropriate. If a particular member did not have established care already, Magellan provided referral information for an obstetrician-gynecologist (OB-GYN) in the member's area. Finally, clinical pharmacists sought to "close the loop" by conducting provider follow-up to relay member interest in contraceptive therapy and member follow-up to ensure an office visit was scheduled, as well as obtain results of the evaluation.

The initial outreach strategy consisted of four aspects: surveys, telephonic outreach, provider follow-up, and fax materials. The surveys were conducted via pre- and post-telephonic outreach in order to properly tailor outreach messages to help prescribers navigate the barriers to prescribing contraceptives, including LARCs. Telephonic outreach was performed to gain insight into the number of patient-specific opportunities available for contraceptive products and to further understand challenges that persist. Fax materials included patient-specific letters and the pre-telephonic survey and OB-GYN referral list upon request. Finally, the Magellan clinical team implemented direct provider communication, education, and support, utilizing key messages and fax materials in an effort to continuously identify challenges and barriers to prescribing.

By engaging directly with patients and facilitating proper communication with providers, this program sought to streamline the process of contraceptive education, evaluation, and, ultimately, utilization.

Preliminary Program Results

Full program results are not yet available; however, interim results have demonstrated an increase in utilization from commencement of the outreach program through the outreach period. Additionally, preliminary analyses of identified challenges regarding contraceptive utilization are summarized in Table 1. Solutions to the identified challenges are also listed in Table 1. Once available, program statistics, successes, and learnings may be shared in a future issue of this publication.

TABLE 1. ONGOING CHALLENGES AND POTENTIAL SOLUTIONS FOR CONTRACEPTIVE UTILIZATION PROGRAM

Challenges – Ongoing	Solutions – Sustained Efforts
Healthcare providers (HCPs) are unaware of patient oral contraceptive nonadherence	Communicate adherence data to HCPs for their MCC Florida patients
Primary care practitioners (PCPs) require additional training concerning alternative methods of contraception	Offer necessary training where appropriate; provide OB-GYN referral list if needed
Providers do not prescribe certain contraceptives because of potential complications associated with usage	Update prescribers with safety information for contraceptives, including prevalence of associated complications and best methods for safe utilization
Providers offer alternative methods of contraception as options but ultimately leave the decision up to the patients	Remind HCPs that target patients have been identified for oral contraceptive nonadherence; provide HCPs with talking points and education opportunities for patients regarding alternative methods of contraception
Providers are uncomfortable with associated overhead cost; believe to be at financial risk	Explain that MCC provides 100% reimbursement through buy-and-bill; provide pharmacy benefit coverage
PCPs see patients infrequently — other health conditions take priority or patients fall out of care	Incorporate Magellan Clinical Outreach Team for direct patient outreach to provide education, encourage follow-up with HCPs, and/or reestablish care
Patients are currently breastfeeding; prescribers are unaware of safety of alternative methods of contraception during breastfeeding	Education regarding contraception safety during breastfeeding

Impact on Medicaid Plans

The preliminary results of this program are notable and timely as the federal government urged state Medicaid programs to increase the appropriate use of contraceptive therapies, particularly LARCs.[12] The Centers for Medicare & Medicaid Services (CMS) issued a bulletin in 2016 highlighting the expansion of LARC use by 12 states that implemented policies that would reimburse providers separately for LARCs immediately following labor and delivery.[12] These policies were implemented in an effort to lift the previous restrictions under state Medicaid policies that were preventing providers from being able to be reimbursed for delivering these services while the woman was inpatient and ultimately resulting in a low utilization rate of LARCs among women.[12] Providers were typically receiving bundled payments from Medicaid for labor and delivery services, and since it is more efficient to insert an IUD or hormonal implant immediately following delivery, providers were not being offered additional reimbursement for this service, thereby deterring them from providing this service.[12] The results of this program are encouraging and may aid in addressing high rates of UIPs among patients with various types of insurance, including Medicaid coverage.

The preliminary results of this program are notable and timely as the federal government urged state Medicaid programs to increase the appropriate use of contraceptive therapies, particularly LARCs.

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Hepatitis C:

Treatment Landscape Update

The hepatitis C virus (HCV) treatment landscape has expanded yet again, with two new Food and Drug Administration (FDA) approvals in 2017: Vosevi™ (Gilead Sciences; sofosbuvir/velpatasvir/voxilaprevir) and Mavyret™ (AbbVie; glecaprevir/pibrentasvir).

In July, the FDA approved Vosevi™, a 12-week, once-daily regimen for patients with chronic HCV genotypes 1 through 6 without cirrhosis or with mild cirrhosis.[1] The approval of Vosevi™ marked the first FDA-approved treatment for patients who have previously been treated with sofosbuvir or other drugs for the treatment of HCV that inhibit NS5A and NS3.[1] The safety and efficacy of Vosevi™ were evaluated in two phase III clinical trials conducted in patients without cirrhosis or with mild cirrhosis.[1] In the first trial, treatment with 12 weeks of Vosevi™ was compared to placebo in adults with HCV genotype 1 who had previously failed treatment with an NS5A inhibitor.[1] Patients with genotypes 2, 3, 4, 5, and 6 received Vosevi™. In the second trial, treatment with 12 weeks of Vosevi™ was compared to treatment with sofosbuvir and velpatasvir Epclusa® (Gilead Sciences) in patients with genotypes 1, 2, or 3 who had failed treatment with sofosbuvir, but not an NS5A inhibitor.[1] In both trials, 96 to 97% of patients who received treatment with Vosevi™ had sustained viral response (SVR) at 12 weeks.[1]

Shortly thereafter, the FDA approved Mavyret™, an eight-week, once-daily regimen for patients with chronic HCV genotypes 1 through 6 without cirrhosis or with mild cirrhosis, including those with moderate to severe kidney disease, including those on dialysis.[2] Additionally, Mavyret™ is indicated for the treatment of HCV genotype 1 in patients who were previously treated with either an NS5A inhibitor or an NS3/4A protease inhibitor, but not both.[2] The safety and efficacy of Mavyret™ were evaluated in clinical trials conducted among patients with chronic HCV genotypes 1 through 6 without cirrhosis or with mild cirrhosis.[2] Twelve weeks following treatment cessation, patients who received treatment with Mavyret™ had an overall SVR of 98%, regardless of treatment duration (8, 12, or 16 weeks).[2] Mavyret™ currently has the lowest pricing for a curative HCV treatment, with a $26,400 price tag for an eight-week course of treatment.[3,4] Given the approved label for Mavyret™, most patients are expected to be treated with an eight-week treatment course.

Vosevi™ and Mavyret™ join Epclusa®, Harvoni® (Gilead Sciences), Technivie™ (AbbVie), Viekira XR™ (AbbVie), and Zepatier® (Merck) in the combination direct-acting antiviral (DAA) oral product landscape. Single-agent oral products are also available, and these include Daklinza™ (Bristol-Myers Squibb), Olysio® (Janssen Therapeutics), and Sovaldi® (Gilead Sciences). However, given that the single-agent products are required to be used in combination with other DAAs and/or ribavirin and that various combination DAA regimens are available, single-agent products have fallen into relative disuse in the current market compared to combination products.

With so many products on the market, competition has driven HCV drug prices down, and manufacturers have positioned themselves in unique ways, such as with lower costs, shorter durations of treatment, and the ability to use therapies in specific patient populations (e.g. severe renal impairment, decompensated cirrhosis, previous NS5A inhibitor failure). The ability to use specific therapies in unique patient populations, particularly in patients with severe renal impairment or decompensated cirrhosis, is important because the HCV patient population is not homogenous. Of note, manufacturer data and other studies have indicated that 7.5% of patients infected with HCV have chronic kidney disease (CKD) stage 4/5, 9% of patients on hemodialysis have HCV infection, and approximately 2.6% of patients with HCV have decompensated cirrhosis.[5,6] Furthermore, of the 1.45 million individuals in the U.S. who are likely to be treated with DAA regimens between 2014 and 2020, an estimated 7.3% will fail treatment, 59% of which will be NS5A inhibitor failures and 52% of which will be non-cirrhotic patients.[7]

Tables 1 and 2 list the manufacturer, mechanism of action, genotype coverage, pill count, data for use in the presence of NS5A inhibitor failure, requirement for concomitant ribavirin use, ability to use in decompensated cirrhosis, ability to use in severe renal impairment, duration of treatment, and cost per treatment course (i.e., cost per cure).

TABLE 1. COMBINATION DAA ORAL PRODUCTS[1,2,4,8-12]

	Epclusa® (sofosbuvir, velpatasvir)	**Harvoni®** (ledipasvir/ sofosbuvir)	**Mavyret™** (glecaprevir/ pibrentasvir)	**Technivie™** (ombitasvir/ paritaprevir/ ritonavir)	**Viekira XR™** (dasabuvir/ ombitasvir/ paritaprevir/ ritonavir)	**Vosevi™** (sofosbuvir/ velpatasvir/ voxilaprevir)	**Zepatier®** (elbasvir, grazoprevir)
Manufacturer	Gilead Sciences	Gilead Sciences	AbbVie	AbbVie	AbbVie	Gilead Sciences	Merck
MOA	NS5A + NS5B	NS5A + NS5B	NS3/4A + NS5A	NS5A + NS3/4A + PK booster	NS5A + NS5B + NS3/4A + PK booster	NS3/4A + NS5A + NS5B	NS3/4A + NS5A
Genotypes covered	①②③④⑤⑥	①④⑤⑥	①②③④⑤⑥	④	①	①②③④⑤⑥	①④
Pill count	1 pill once daily	1 pill once daily	3-pill blister pack once daily	2 pills once daily	3 pills once daily	1 pill once daily	1 pill once daily
Genotypes covered by 8-week duration of therapy	N/A	❶	①②③④⑤⑥	N/A	N/A	N/A	N/A
Data in NS5A inhibitor failures	No	No	Yes*	No	No	Yes	No
Requirement for concomitant ribavirin use	Yes: decompensated cirrhosis	Yes: treatment-experienced cirrhotics, decompensated cirrhosis	No	Ribavirin must be used in patients with genotype 4 without cirrhosis or without compensated cirrhosis; ribavirin is not necessary for patients who are treatment-naïve without cirrhosis and who cannot take or tolerate ribavirin	Ribavirin must be used in patients with genotype 1a without cirrhosis or genotype 1a with compensated cirrhosis; ribavirin is not necessary for patients with genotype 1b ± compensated cirrhosis	No	Yes: Genotype 1a with resistance and genotypes 1 and 4 P/R-experienced
Ability to use in decompensated cirrhosis	Yes	Yes	No	No	No	No	No
Ability to use in severe renal impairment	No dose recommendation in severe CKD	No dose recommendation in severe CKD	Yes	No dosage adjustment required in severe renal impairment; not studied in patients on dialysis	No dosage adjustment required in severe renal impairment, including those on dialysis	No dose recommendation in severe CKD	Yes
Duration of treatment	12 weeks	8 to 12 to 24 weeks	8 to 12 to 16 weeks	12 weeks	12 to 24 weeks	12 weeks	12 to 16 weeks
Cost per treatment course (WAC)	$74,760	$63,000 to $94,500 to $189,000	$26,400 to $39,600 to $52,800	$76,653 ± cost of ribavirin	$83,319 to $166,638 ± cost of ribavirin	$74,760	$54,600 to $72,800

KEY

◯ Genotypes each therapy can be used in without special circumstances.

● Additional considerations: eight week-duration Harvoni® can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pretreatment HCV RNA <6 million IU/mL.

*Prior NS5A experience or PI experience, but not both.

Abbreviations: CKD = chronic kidney disease; DAA = direct-acting antiviral; MOA = mechanism of action; P/R = pegylated interferon and ribavirin; PK = pharmacokinetics; WAC = wholesale acquisition cost (WAC as of 8/11/17). Note: Pricing is not provided in this table for alternative regimens utilizing interferon.

TABLE 2. SINGLE-AGENT ORAL PRODUCTS[4,13-15]

	Daklinza™ (daclatasvir)	Olysio® (simeprevir)	Sovaldi® (sofosbuvir)
Manufacturer	Bristol-Myers Squibb	Janssen Therapeutics	Gilead Sciences
MOA	NS5A	NS3/4A	NS5B
Genotypes covered	N/A	N/A	N/A
Pill count	1 pill once daily + sofosbuvir ± ribavirin	1 capsule once daily + sofosbuvir for genotype 1 without cirrhosis or with compensated cirrhosis 1 capsule once daily + peg-IFN-alfa + ribavirin for genotypes 1 and 4 without cirrhosis or with compensated cirrhosis ± HIV coinfection	1 pill once daily + ribavirin for genotypes 2 and 3 1 pill once daily + peg-IFN-alfa + ribavirin for genotypes 1 and 4
Genotypes covered by 8-week duration of therapy	N/A	N/A	N/A
Data in NS5A inhibitor failures	No	No cross-resistance is expected between DAA agents with different MOAs; simeprevir remained fully active against substitutions associated with resistance to NS5A inhibitors, NS5B nucleoside, and non-nucleoside polymerase inhibitors	Sofosbuvir was active against HCV replicons with NS3/4A protease inhibitor, NS5B non-nucleoside inhibitor, and NS5A inhibitor-resistant variants
Requirement for concomitant ribavirin use	± ribavirin	Ribavirin must be used in patients with genotypes 1 or 4 without cirrhosis or with compensated cirrhosis (in addition to peg-IFN-alfa); not required in patients with genotype 1 without cirrhosis or with compensated cirrhosis	Yes
Ability to use in decompensated cirrhosis	Yes	No	No
Ability to use in severe renal impairment	No dosage adjustment necessary with any degree of renal impairment	Not studied in severe renal impairment or ESRD, including patients requiring dialysis	No dose recommendation in severe CKD; safety and efficacy not established in patients with severe renal impairment or ESRD requiring dialysis
Duration of treatment	12 weeks	12 to 24 weeks	12 to 24 weeks
Cost per treatment course (WAC)	$63,000 ± cost of ribavirin	$150,360 (includes cost of sofosbuvir)	$84,000 to $168,000 + cost of ribavirin

Abbreviations: CKD = chronic kidney disease; DAA = direct-acting antiviral; ESRD = end-stage renal disease; MOA = mechanism of action; peg-IFN-alfa = pegylated interferon alfa; WAC = wholesale acquisition cost (WAC as of 8/11/17). Note: Pricing is not provided in this table for alternative regimens utilizing interferon.

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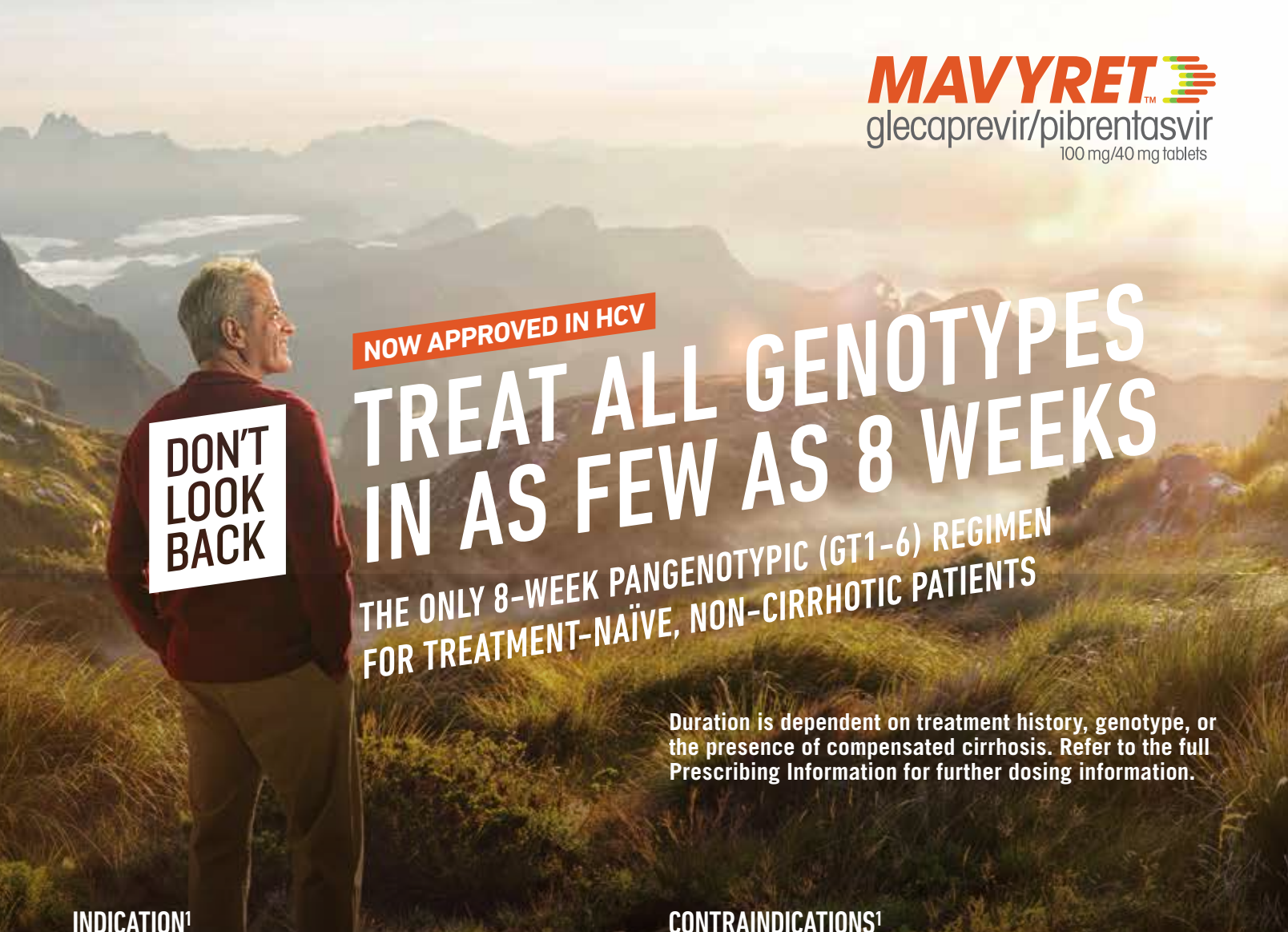
MAVYRET™
glecaprevir/pibrentasvir
100 mg/40 mg tablets



NOW APPROVED IN 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.

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

abbvie

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.

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.
Antimycobacterials:		
Rifampin	↓ glecaprevir ↓ pibrentasvir	Coadministration is contraindicated because of potential loss of therapeutic effect *[see Contraindications]*.
Concomitant Drug Class: Drug Name	**Effect on Concentration**	**Clinical Comments**
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.

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Plaque Psoriasis:

IL-23 Treatment Landscape and Pipeline Update

Interleukin-23 (IL-23) is a pro-inflammatory cytokine that plays a large role in autoimmunity.[1] IL-23 is found in the skin, bowel walls, and synovial membranes of patients with plaque psoriasis (PsO), chronic inflammatory bowel disease, and rheumatoid arthritis, respectively.[1] Over the past few years, IL-23 has been identified as a target for inflammatory diseases.[1] Although IL-23 can be targeted using an interleukin-12 (IL-12) or IL-23 directed antibody, the p19 subunit (IL-23p19) and IL-23 receptor are the most useful drug targets to avoid the modification of IL-12 effects.[2]

Recently the Food and Drug Administration (FDA) approved TREMFYA™ (guselkumab; Janssen Biotech Inc.), the first biologic therapy that selectively blocks IL-23.[3] Guselkumab is indicated for the treatment of adults living with moderate to severe PsO who are candidates for systemic therapy or phototherapy.[4] The approval of guselkumab was based on the results from the phase III VOYAGE 1, VOYAGE 2, and NAVIGATE trials.[3] In VOYAGE 1 and VOYAGE 2, treatment with guselkumab demonstrated significant efficacy in patients with moderate to severe PsO compared to treatment with placebo or Humira® (adalimumab; AbbVie).[3] At week 24, more than seven out of 10 patients treated with guselkumab reported achieving Psoriasis Area and Severity Index (PASI) 90 (i.e., a 90% improvement from baseline) compared to more than four out of 10 patients treated with adalimumab.[3,4] In NAVIGATE, 31% of patients treated with guselkumab were considered cleared or almost cleared at week 28 compared to 14% of patients treated with Stelara® (ustekinumab; Janssen Biotech Inc.) 12 weeks after randomization to continue guselkumab or ustekinumab.[3,4]

Other IL-23 drugs in late-stage development include tildrakizumab (Sun Pharmaceutical Industries) and risankizumab (AbbVie, Boehringer Ingelheim), which are both being studied for the treatment of moderate to severe PsO.[5,6] The manufacturer filed a biologics license application (BLA) for tildrakizumab earlier this year, and the FDA accepted the BLA submission in May 2017.[7] The BLA submission was based on the results of two pivotal phase III trials, RESURFACE 1 and 2, which demonstrated that a higher number of patients treated with tildrakizumab achieved PASI 90 and 100 compared to placebo and Enbrel® (etanercept; Amgen).[5,7] More specifically, 54% and 59% of patients treated with tildrakizumab 100 mg and 200 mg, respectively, achieved PASI 90 at week 28 compared to 31% of patients treated with etanercept.[5] Although the manufacturer has declined to disclose the Prescription Drug User Fee Act date for tildrakizumab, an estimated decision time frame of March to April 2018 is expected based on the BLA acceptance date.[8]

Risankizumab is currently in phase III trials for PsO and is also in mid-stage development for the treatment of psoriatic arthritis and Crohn's disease.[9] In a phase II trial comparing treatment with risankizumab to ustekinumab, patients treated with risankizumab achieved superior clinical responses compared to patients treated with ustekinumab.[6] At week 12, 77% of patients treated with risankizumab achieved PASI 90 or greater compared to 40% of patients treated with ustekinumab ($P<0.001$).[6] There are four ongoing phase III

TABLE 1. IL-23 INHIBITORS			
	Guselkumab (TREMFYA™)	**Risankizumab**	**Tildrakizumab**
Manufacturer	Janssen Biotech Inc.	AbbVie, Boehringer Ingelheim	Sun Pharmaceutical Industries
FDA Approval Status	FDA-approved	BLA accepted; decision pending	Phase III trials ongoing
MOA	IL-23p19 inhibitor	IL-23p19 inhibitor	IL-23p19 inhibitor
Dosing schedule	Week 0, week 4, and every 8 weeks thereafter	Once every 12 weeks	Once every 12 weeks

Abbreviations: BLA = biologics license application; FDA = Food and Drug Administration; MOA = mechanism of action

trials for risankizumab — UltiMMa-1, UltiMMa-2, IMMhance, and IMMvent — which have anticipated data readouts later this year.[10] UltiMMa 1 and 2 are head-to-head comparator trials that are designed to evaluate the safety and efficacy of risankizumab compared to ustekinumab.[10] IMMhance will evaluate the effects of withdrawal and retreatment with risankizumab among patients with moderate to severe PsO.[10] IMMvent is designed to compare risankizumab to adalimumab among patients with moderate to severe PsO.[10]

Although guselkumab represents the first IL-23 directed antibody to reach the U.S. market, tildrakizumab and risankizumab still have the potential to be transformative therapies due to their more convenient, once-every-12-weeks administration schedules compared to available biologics for PsO, which must be dosed every 2, 4, or 8 weeks. A summary of the three aforementioned IL-23 inhibitors is provided in Table 1.

Before the discovery of IL-23 as a target for autoimmune diseases, tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17) represented the primary targets for biologic therapies. Based on the results of the phase III trials described on the previous page, IL-23 inhibitors may offer superior efficacy compared to TNF-α inhibitors and monoclonal antibodies that target both IL-12 and IL-23 (i.e., ustekinumab).[11] Thus far, there have been no head-to-head trials comparing IL-23 inhibitors and IL-17 inhibitors (brodalumab [SILIQ™; Valeant Pharmaceuticals], ixekizumab [Taltz®; Eli Lilly and Company], and secukinumab [Cosentyx®; Novartis]), which have demonstrated very high clearance rates in PsO. However, it is likely that IL-23 inhibitors will compete with IL-17 inhibitors in the PsO space and potentially other autoimmune categories in the coming years.

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Biologics in Asthma:

A Pipeline Update

The Food and Drug Administration (FDA) approval of omalizumab (Xolair®, Genentech and Novartis) marked the first biologic approval for the treatment of asthma.[1] Omalizumab received approval for the treatment of severe, persistent, allergic asthma in patients 12 years of age and older.[1] More than 10 years later, mepolizumab (Nucala®, GlaxoSmithKline) and reslizumab (Cinqair®, Teva) were approved for the treatment of asthma, but for a different patient group: patients with severe asthma with eosinophilic inflammation.[1]

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Since then, manufacturers have continued to focus their asthma research and development efforts on targeting the primary cause of the disease and identifying immunomodulators that provide individualized therapy. There are a number of asthma biologics in ongoing phase III clinical trials, including benralizumab (AstraZeneca), dupilumab (Dupixent®, Sanofi Genzyme and Regeneron), and tralokinumab (AstraZeneca, MedImmune), which are discussed below.

Benralizumab

Benralizumab, an interleukin-5 (IL-5) inhibitor, is being studied for the treatment of severe, uncontrolled asthma. The safety and efficacy of benralizumab were studied in the phase III ZONDA trial, which demonstrated that the addition of benralizumab to standard of care allowed oral corticosteroid (OCS)-dependent patients to significantly reduce or discontinue steroids while maintaining control of their asthma.[2] The study met its primary endpoint by demonstrating a statistically significant and clinically relevant reduction in daily maintenance OCS use in two benralizumab dosing arms compared to placebo.[2] Patients who were treated with benralizumab were four times more likely to reduce their OCS dose compared to the placebo group, with median OCS dose reductions of 75% and 25% in the benralizumab and placebo groups, respectively.[2] In addition to steroid dose reductions, patients treated with benralizumab achieved both a 70% reduction in overall annual exacerbation rates and a 93% reduction in exacerbations requiring emergency room visits or hospitalizations compared to placebo.[2]

Benralizumab was also studied in the pivotal phase III SIROCCO and CALIMA trials, the results of which demonstrated that treatment with benralizumab significantly decreased the annual rate of asthma exacerbations over 48 weeks by up to 45% and 51% when given every four and eight weeks, respectively, compared to placebo.[3] In SIROCCO and CALIMA, an improvement in forced

expiratory volume at 1 second (FEV1) was observed in both dosages of benralizumab, but asthma symptoms were improved only in the every eight-week regimen.[3] All three studies — ZONDA, SIROCCO, and CALIMA — were included in the biologics license application (BLA) submission to the FDA, and a decision is expected in the fourth quarter of 2017.[3]

Dupilumab

Dupilumab, an interleukin-4 (IL-4) inhibitor, targets the messenger proteins of eosinophils, rather than the eosinophils themselves.[1] The safety and efficacy of dupilumab are being evaluated in phase III trials: VENTURE, VOYAGE, LIBERTY ASTHMA QUEST, and LIBERTY ASTHMA TRAVERSE.[4] The results of VENTURE (severe, steroid-dependent asthma) are expected later this year, and the results of LIBERTY ASTHMA TRAVERSE (long-term phase II/III safety and tolerability study) and VOYAGE (uncontrolled asthma in children) are expected in 2019 and 2020, respectively.[4] The results of LIBERTY ASTHMA QUEST (persistent asthma) were recently announced; and treatment with dupilumab, when added to standard therapies, was found to reduce severe asthma attacks and improve lung function.

Dupilumab was previously studied in a phase IIb trial in adult patients with moderate to severe asthma whose disease is uncontrolled despite treatment with inhaled corticosteroids (ICS) and long-acting beta agonists (LABA).[5] The study met its primary endpoint of improving lung function in patients with high blood eosinophil counts (HEos), and positive results were reported for secondary endpoints in patients with low blood eosinophil counts (LEos).[5]

In patients with HEos, those treated with dupilumab 200 mg or 300 mg every other week (Q2W) in combination with ICS/LABA demonstrated a statistically significant 12-15% improvement in FEV1 at week 12 and a 64-75% improvement in the annualized rate of severe exacerbations compared to placebo.[5] In patients with LEos, patients treated with dupilumab 200 mg or 300 mg Q2W demonstrated a greater than 8% improvement in FEV1 at week 12 ($P<0.001$) compared to placebo, both in combination with ICS/LABA.[5] Furthermore, patients in the dupilumab 200 mg and 300 mg Q2W dosing arms in combination with ICS/LABA demonstrated 68% and 62% reductions, respectively, in the annualized rate of severe exacerbations ($P<0.01$ and $P<0.05$, respectively) compared to placebo in combination with ICS/LABA.[5] In a presentation to investors earlier this year, Regeneron indicated that a BLA submission could take place in the fourth quarter of 2017.[6] Dupilumab is currently FDA-approved for the treatment of atopic dermatitis.

Tralokinumab

Tralokinumab, an interleukin-13 (IL-13) antibody, is being studied for the treatment of patients with severe, uncontrolled asthma.[7] Earlier this year, the manufacturers announced that the phase III STRATOS 1 study did not meet its primary endpoint of a significant reduction in the annual asthma exacerbation rate compared to placebo.[7] STRATOS 1 represents one of two pivotal phase III trials in which the drug is being studied. The ongoing STRATOS 2 trial will evaluate the safety and efficacy of tralokinumab in a subpopulation of patients identified in STRATOS 1: patients with an elevated biomarker associated with increased IL-13 activity.[7]

Treatment with tralokinumab is also being studied in the TROPOS, MESOS, and Japan Long-Term Safety (LTS) trials.[7] The results of STRATOS 2 (uncontrolled asthma in adults and adolescents), TROPOS (OCS-dependent asthma in adults and adolescents), and MESOS (asthma that is inadequately controlled on corticosteroids) are expected in 2017, and the results of the Japan LTS trial (asthma that is inadequately controlled on ICS/LABA) are expected in 2018.[4] The manufacturers have indicated that potential future regulatory submissions for tralokinumab will be dependent on the results of STRATOS 1 and 2.[7]

Phase III Trial Discontinuations

The IL-13 inhibitor, lebrikizumab (Roche), was previously in phase III development; however, the manufacturer discontinued asthma trials for the drug

TABLE 1. BIOLOGICS IN PHASE III DEVELOPMENT FOR ASTHMA

	Benralizumab	Dupilumab	Tralokinumab
Manufacturer(s)	AstraZeneca	Sanofi Genzyme and Regeneron	AstraZeneca, MedImmune
Regulatory Status	PDUFA Q4 2017	Potential BLA submission in Q4 2017 Currently FDA-approved for AD	BLA submission will depend on phase III trial results, which are expected later this year
MOA	IL-5 inhibitor	IL-4 inhibitor	IL-13 inhibitor

Abbreviations: AD = atopic dermatitis; BLA = Biologics License Application; FDA = Food and Drug Administration; IL = interleukin; MOA = mechanism of action; PDUFA = Prescription Drug User Fee Act; Q4 = fourth quarter

in 2016 based on mixed results of the pivotal phase III LAVOLTA I and II studies.[8] Rights to lebrikizumab were out-licensed to Dermira in 2017 to begin clinical trials in atopic dermatitis.[9]

NONBIOLOGIC, NOVEL THERAPIES TO WATCH

Fevipiprant

Fevipiprant (Novartis), an oral prostaglandin D_2 receptor antagonist, is an investigational therapy being developed for the treatment of moderate to severe asthma and sputum eosinophilia.[10] Fevipiprant represents a novel approach to asthma management in that it is the first investigational agent to utilize a dual pathway approach: the inhibition of eosinophils while stopping airway lining inflammation and repairing damage.[11] The safety and efficacy of fevipiprant are being evaluated in two ongoing phase III trials, LUSTER1 and LUSTER2, in patients with severe asthma stratified by blood eosinophils.[11]

In a phase II trial, treatment with fevipiprant reduced eosinophilic airway inflammation, was well tolerated by patients with persistent, moderate to severe asthma, and increased sputum eosinophil counts despite treatment with ICS.[12] If approved, fevipiprant would likely be used as a pre-biologic, add-on maintenance treatment in patients with severe asthma with an eosinophilic phenotype whose disease is not adequately controlled by standard of care treatment.[11] Phase III trials are ongoing, but the manufacturer has indicated that filing could occur as early as 2019.[11]

Timapiprant

Timapiprant (Elevanta Ltd., Oxagen Limited), formerly OC000459, is a chemoattractant receptor expressed on T-helper type 2 cells (CRTH2) antagonist that is being investigated for the treatment of atopic eosinophilic asthma in adults.[13] The safety and efficacy of timapiprant are being evaluated in an ongoing phase III clinical study that is being conducted across 21 centers in Russia.[13]

A phase II study that evaluated twice-daily timapiprant 200 mg demonstrated that treatment with timapiprant significantly improved quality of life and nocturnal symptoms compared to placebo in patients with moderate persistent asthma (P=0.0113 and P=0.008, respectively).[14] Improvements in FEV1 and sputum eosinophil count were not statistically significant.[14] In a phase II crossover study, treatment with twice-daily timapiprant 200 mg demonstrated significant inhibition of late asthmatic response to allergen challenge and significant reductions in post-allergen increase in sputum eosinophils (P=0.018 and P=0.002, respectively).[14] At this time, information about an estimated phase III study completion date and potential new drug application (NDA) submission is unavailable.

TABLE 2. NONBIOLOGIC, NOVEL THERAPIES IN PHASE III DEVELOPMENT FOR ASTHMA

	Fevipiprant	Timapiprant
Manufacturer(s)	Novartis	Elevanta Ltd., Oxagen Limited
Regulatory Status	NDA filing could begin in 2019	NDA submission timeline unavailable
MOA	Oral prostaglandin D_2 receptor antagonist	CRTH2 antagonist

Abbreviations: CRTH2 = chemoattractant receptor expressed on T-helper type 2 cells; MOA = mechanism of action; NDA = new drug application

As many as 315 million patients worldwide have asthma, with up to 10% of patients having severe asthma.

Conclusion

As many as 315 million patients worldwide have asthma, with up to 10% of patients having severe asthma.[15-17] Despite high doses of standard-of-care medications, some patients experience uncontrolled, severe asthma, which can be debilitating and potentially fatal among patients who experience frequent exacerbations, substantial lung function limitations, and significant negative impact on their quality of life.[18] Of note, patients with severe asthma account for 50% of asthma-related costs.[19] If approved, these investigational biologics and nonbiologic, novel therapies could transform the asthma treatment landscape by offering effective therapies for patients whose disease remains uncontrolled by standard of care asthma controller medications, and, in effect, potentially reduce the

number of asthma-related exacerbations and hospitalizations, while also improving quality of life for this patient population.

Although not yet in phase III development, tezepelumab (AstraZeneca and Amgen Inc.) was recently studied in a phase IIb trial in patients with severe, uncontrolled asthma.[20] The study met its primary endpoint by demonstrating annual asthma exacerbation rate reductions of 61%, 71%, and 66% in the tezepelumab 70 mg every four weeks (Q4W), 210 mg Q4W, and 280 mg Q2W treatment arms, respectively, compared to placebo ($P<0.001$ for all).[20] Significant and clinically relevant exacerbation rate reductions were observed independent of baseline blood eosinophil count or other type 2 inflammatory biomarkers.[20] Although tezepelumab has not yet progressed to phase III trials, it is possible that this investigational agent may soon join benralizumab, dupilumab, and tralokinumab as notable biologic therapies in phase III development for asthma. In conclusion, payors are encouraged to keep a watchful eye on these potentially transformative therapies as they approach regulatory submission and decision-making dates to prepare for the possible paradigm shift in asthma management.

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PIPELINE DRUG LIST

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
testosterone enanthate (QuickShot® Testosterone)	Antares Pharma Inc.	Hypogonadism	SC	Submitted	10/20/2017
golimumab (Simponi Aria® [IV])	Johnson & Johnson	axSPA; PsA	IV	Submitted	10/20/2017
eculizumab (Soliris®)	Alexion Pharmaceuticals Inc.	MG	IV	Orphan drug	10/23/2017
ataluren (Translarna™)	PTC Therapeutics Inc.	DMD	Oral	Orphan drug; fast track	10/24/2017
rivaroxaban (Xarelto®)	Johnson & Johnson	VTE	Oral	Priority review	10/27/2017
ferric citrate (Auryxia®)	Keryx Biopharmaceuticals Inc.	Anemia due to chronic renal failure, dialysis-independent	Oral	Submitted	11/6/2017
dasatinib (Sprycel®)	Bristol-Myers Squibb Company	CML	Oral	Orphan drug; priority review; fast track	11/9/2017
hepatitis B vaccine (Heplisav-B™)	Dynavax Technologies Corporation	Hepatitis B prevention	IM	Submitted	11/10/2017
aprepitant (Cinvanti™)	Heron Therapeutics Inc.	CINV prevention	IV	Submitted	11/10/2017
rhGUS (UX003)	Ultragenyx Pharmaceutical Inc.	MPS VII; Sly syndrome	IV	Orphan drug; fast track; priority review	11/16/2017
axicabtagene ciloleucel (KTE-C19)	Kite Pharma Inc.	DLBCL - NHL	IV	Orphan drug; breakthrough therapy; priority review	11/29/2017
evolocumab (Repatha®)	Amgen Inc.	Dyslipidemia/ Hypercholesterolemia	SC	Orphan drug; priority review	12/2/2017
ethinyl estradiol/ levonorgestrel (Twirla®)	Agile Therapeutics Inc.	Contraception	Transdermal	Resubmitted after CRL	12/26/2017
testosterone undecanoate (Jatenzo®)	Clarus Therapeutics Inc.	Hypogonadism	Oral	Submitted	12/26/2017

PIPELINE DRUG LIST

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
ivabradine (Corlanor®)	Amgen Inc.	CHF and cardiomyopathies	Oral	Submitted	Q4, 2017
cinacalcet (Sensipar®)	Amgen Inc.	Hyperparathyroidism (pediatrics)	Oral	Orphan drug	Q4, 2017
ertugliflozin	Merck & Co. Inc.	T2DM	Oral	Submitted	December, 2017
ertugliflozin/metformin	Merck & Co. Inc.	T2DM	Oral	Submitted	December, 2017
ertugliflozin/sitagliptin	Merck & Co. Inc.	T2DM	Oral	Submitted	December, 2017
tofacitinib citrate (Xeljanz®/Xeljanz® XR)	Pfizer Inc.	PsA	Oral	Submitted	December, 2017
voretigene neparvovec (LUXTURNA™)	Spark Therapeutics Inc.	IRD (biallelic RPE65-mediated)	Intraocular	Orphan drug; breakthrough therapy; priority review	1/12/2018
buprenorphine depot (CAM2038)	Apple Tree Partners	SUD	SC	Fast track	1/19/2018
plecanatide (Trulance™)	Synergy Pharmaceuticals Inc.	IBS	Oral	Submitted	1/29/2018
abemaciclib	Eli Lilly and Company	Breast cancer	Oral	Breakthrough therapy; priority review	Q1, 2018
epinephrine auto-injector (Auvi-Q® 0.1 mg)	Kaléo	Anaphylaxis in infants, small children	IM/SC	Priority review	1/26/2018
infliximab, biosimilar	Pfizer Inc.	RA; CD; psoriasis; UC; PsA; axSPA	IV	Submitted	December, 2017 to January, 2018
sunitinib malate (Sutent®)	Pfizer Inc.	RCC	Oral	Fast track	January, 2018

Abbreviations: axSPA = axial spondyloarthritis; CD = Crohn's disease; CHF = congestive heart failure; CINV = chemotherapy-induced nausea and vomiting; CML = chronic myelogenous leukemia; CRL = complete response letter; DLBCL = diffuse large B-cell lymphoma; DMD = Duchenne muscular dystrophy; IBS = irritable bowel syndrome; IRD = inherited retinal diseases; IV = intravenous; MG = myasthenia gravis; MPS VII = mucopolysaccharidosis VII; NHL = non-Hodgkin's lymphoma; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RCC = renal cell carcinoma; rhGUS = recombinant human beta-glucuronidase; SC = subcutaneous; SUD = substance use disorder; T2DM = type 2 diabetes mellitus; UC = ulcerative colitis; VTE = venous thromboembolism

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Make a difference

Over the last half-century, we have brought together a family of innovative pharmaceutical companies all with one overarching mission: to address and solve some of the most important unmet medical needs of our time.

Janssen companies are focused on developing groundbreaking treatments in 5 major therapeutic areas: Neuroscience, Infectious Diseases, Oncology, Immunology, and Cardiovascular/Metabolism, and our product portfolio addresses other critical areas as well.

We are people helping people — we work closely together to harness our combined knowledge and resources, leverage the power and promise of outstanding science, and enhance the length and quality of life for people throughout the world.

At Janssen, we passionately pursue science for the benefit of patients everywhere.

Mario Mesa, *Social Fire*
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