Summer 2016

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

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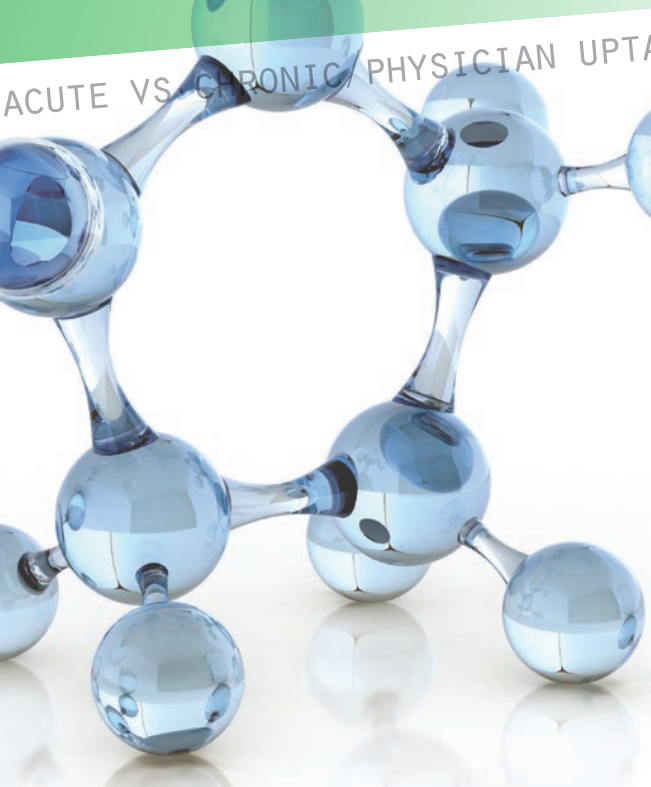
REFERENCE BIOSIMILAR

ACUTE VS CHRONIC/PHYSICIAN UPTAKE • CLINICAL COMPARABILITY/ECONOMICS/FORMULARY DESIGN



Biosimilars: Overcoming Challenges to Ensure Cost-Effective Care

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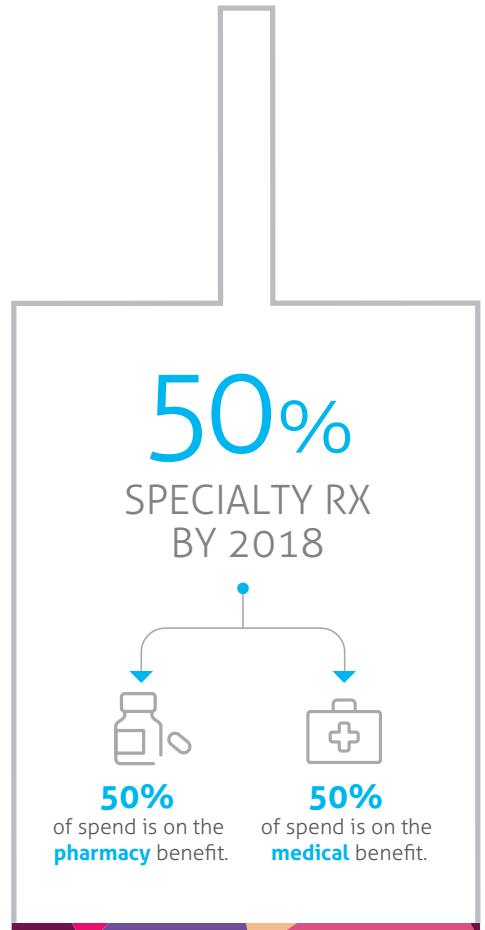

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Welcome to the **Magellan Rx** Report

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Features

Trends

Mostafa Kamal

Dear Managed Care Colleagues,

Welcome to our summer issue of the *Magellan Rx Report*. In this issue we continue focusing on key managed care trends and opportunities — so it is no surprise specialty pharmacy management remains a priority. Clinical and economic considerations demand payor attention as specialty spending continues to grow, within both the medical and pharmacy benefit. The importance of specialty management will only increase as more first-in-class, groundbreaking therapies promise to reach the market in the not-so-distant future.

The clinical opportunities associated with these therapies are accompanied by fiscal and operational challenges. These demand innovative, forward-looking, and insightful management strategies. This issue of the *Magellan Rx Report* includes a summary of some of the key findings of our *Magellan Rx Trend Report*™, setting the stage for discussions of what the next era of specialty management will require. The *Trend Report* looks at the evolution of management and cost trends, including the unique perspective offered when assessing both medical and pharmacy spending and management strategies, as it frames up potential opportunities for the future. Trends in medical formulary management, including product preferencing and site-of-care management are highlighted, giving insight into the evolution and uptake of these strategies and opportunities for the future.

Our medical management strategies article picks up on this theme, as it further explores trends highlighted in the *Trend Report* and provides some real-world perspectives on how payors can proactively establish and implement management solutions that position them for success in the future. The biosimilars article explores the clinical and cost-savings opportunities available as biosimilar entrants make their way to the market and how payors and providers can navigate the integration process, framing up the unique aspects of managing the uptake of these agents.

Additionally, in this issue we delve into the interface of the clinical and financial impact of managing potentially costly clinical conditions. First, we explore the potential role of long-acting injectable antipsychotics as a solution to nonadherence in a potentially vulnerable patient population with significant mental health needs. Meanwhile, our article on multiple myeloma considers the significant economic implications for payors of this relatively rare disease.

Our article "Value-Based PBM — Implications for Various Stakeholders," serves as a capstone to each of the preceding discussions. It explores not only the evolving needs of payors in navigating the increasingly complex dynamics of medical and pharmacy specialty management, but touches upon the shift occurring as payors expect refinement and sophistication in the services they seek from their PBM. The days of robust claims adjudication and formulary management services representing adequate support by a PBM have given way to a new level of service expectations. Value-based services — including outcomes-based contracting, site-of-care management, support around medical management, and data analytics to help achieve success in medical management — identify and address gaps in care, and demonstrate success with clinical programs such as STAR ratings and HEDIS measures are no longer optional, they are essential.

To learn more about Magellan Rx Management and our value-based PBM services, supporting the initiatives of payors 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

BCBSA Report Explores Rising Specialty Pharmacy Costs

According to a new report from the Blue Cross Blue Shield Association (BCBSA) and HealthCore Inc., specialty pharmacy costs per member increased 26 percent from 2013 to 2014. This in-depth report — "The Growth in Specialty Drug Spending from 2013 to 2014" — investigated both medical and pharmacy claims data, each of which account for approximately half of specialty drug spending.

The report also found:

- The total cost of treatment rose for all specialty drug categories studied. Fifteen of the most common or expensive specialty drug categories were studied, including drugs to treat cancer, inflammatory conditions, multiple sclerosis, HIV, and hepatitis.
- The per member increase in specialty drug spending was $87 per year during the study period.
- The rising cost of specialty drugs was the major cause of the increase in spending. The report attributed 15 percent of the 26 percent increase to higher treatment cost. Utilization had less impact, accounting for about 11 percent of the increase.
- In 2014, annual specialty drug spending per member was 17 percent higher in the individual market than in the employer market. The cost of treatment in both markets was similar, but utilization rates varied by condition. Individual members had higher utilization rates for cancer, hepatitis, and HIV, but somewhat lower utilization rates for rheumatoid arthritis, other inflammatory conditions, and multiple sclerosis.

"The recent, rapid increases in specialty drug costs are a concern for everyone — the public, medical professionals, health care companies, employers of all sizes, and taxpayers who bear the cost of prescription drugs provided by government programs such as Medicare, Medicaid, and those who receive financial assistance to purchase individual coverage," said Trent Haywood, MD, chief medical officer for BCBSA. "To promote affordability and access to new innovative medicines, it's important to have greater competition and choice to bring costs down for everyone."

Source: Blue Cross Blue Shield Association examines the growing costs of specialty pharmacy. Blue Cross and Blue Shield Association. News release. May 19, 2016.

Intermountain Healthcare Joins Forces With Top University to Further Precision Health and Medicine

Intermountain Healthcare's Precision Genomics Core Laboratory and the Stanford Genome Technology Center (SGTC) have formed a joint team of researchers, clinicians, and other specialists who will identify strategies to apply cutting-edge technologies to deliver precision health. The team's priorities include using advanced technologies developed at SGTC to identify novel biomarkers, and evaluating the clinical benefits of using molecular analysis as part of patient care.

"This research partnership has the potential for a direct and very positive impact on our ability to extend the lives and improve the quality of life for patients with advanced cancer, among other health issues," said Terri Kane, vice president of Intermountain Healthcare's Southwest Region.

"Conducting our studies in collaboration with Intermountain Healthcare will enable our joint team to address more ambitious clinical research questions on a much broader scale," said Hanlee Ji, MD, senior associate director of SGTC and associate professor at the Stanford University School of Medicine, Division of Oncology.

Source: Intermountain Precision Genomics and Stanford Genome Technology Center form clinical genomics partnership. Intermountain Healthcare. News release. April 19, 2016.

Alternatives Examined for Costly and Potentially Preventable ER Visits

Research released by Excellus BlueCross BlueShield (BCBS) found that 10 common conditions, such as ear infections and sore throats, account for about 2 million annual visits to hospital emergency rooms (ERs) in New York, and cost an estimated $1.3 billion. Researchers say the vast majority of these visits — nine out of 10 — could have been avoided or treated in other health care settings.

Excellus BCBS analyzed the state's ER visit data for New York hospitals in 2013, which included a total of 6.4 million ER visits. The state of New York defines "potentially preventable" ER visits as those that could have been treated elsewhere, or avoided with quicker access to preventive and primary care, or better care coordination.

"Compared to treatment received in a primary care setting, a telemedicine visit, or an urgent care facility, the ER has the longest wait times and highest expenses, including out-of-pocket costs," said Jamie Kerr, MD, medical director, Excellus BCBS. The preferred method of care for nearly all of these cases is for patients to see their primary care physicians for treatment. However, "when the physician isn't available, many of these potentially preventable ER cases can be addressed with telemedicine visits or going to urgent care centers at considerably greater convenience and less cost."

The Excellus analysis showed that when patients' physicians are unavailable, telemedicine is a convenient and cost-effective option for the patients who need treatment for the 10 common conditions.

Source: Alternatives for "potentially preventable" NYS hospital ER visits examined: 2 million common condition visits add up to more than $1.3B in spending. Excellus BlueCross and BlueShield. News release. April 6, 2016.

Priority Health Invests in Program to Prevent Medication Errors

Priority Health is spending nearly $3 million to expand its pharmacy management programs throughout Michigan. It is the first health plan in the state to extend such a program to both its Medicare and employer-sponsored health plans.

Priority Health initially launched a Medication Therapy Management (MTM) pilot program with Medicare members. The program resulted in a savings of $60 per member per month (PMPM) during the first year and $66 PMPM over 24 months. The program resolved an average of two drug-related issues per member. Priority saved $4 in medical costs for every $1 invested in the program.

As part of the expansion, about $2 million is being allocated to local pharmacies where pharmacists help patients understand their prescription drugs, identify potentially dangerous and costly medical errors, and help patients manage out-of-pocket costs. Priority has committed an additional $1 million to incorporate its MTM program into physician practices where in-house pharmacists will be on hand to help patients who have appointments with their doctors.

"This program is another example of Priority Health's continuous effort to look for new ways to make monumental and measurable changes to the way health care is delivered for our members," says Joan Budden, president and CEO of Priority Health.

Source: Priority Health invests nearly $3 million in programs to help Michiganders avoid medication errors. Priority Health. News release. April 11, 2016.

Horizon Partners With Hospital in Value-Based Care Collaborative

Horizon Blue Cross Blue Shield of New Jersey (BCBSNJ) and University Hospital in Newark are creating a strategic partnership to integrate Horizon's patient-centric, value-based care models into the hospital's activities to enhance the health and well-being of residents of Newark and surrounding communities. The goals of the collaboration are to improve the quality of care, reduce overall costs, and enhance patient experience.

Initially, the collaboration will bring Horizon's "Episodes of Care (EOC) for Pregnancy and Delivery" protocols to University Hospital's maternity program. Horizon BCBSNJ's team will work with their counterparts at the hospital to improve all aspects of maternity care, including prenatal care, pregnancy, delivery, postpartum care, and outcomes. They will also develop procedures to reduce the number of preterm deliveries.

Horizon BCBSNJ's EOC for Pregnancy and Delivery has successfully reduced the number of complications, unnecessary cesarean, and postpartum infections. Newly released data on its EOC program, which included more than 8,000 patients and 51 specialists, found that members in EOC practices saw significant benefits when compared with members receiving the same services from non-EOC practices. For example, the EOC patients had higher quality outcomes, lower hospital readmissions, and a 32 percent reduction in unnecessary C-sections. Patient satisfaction for members in the EOC group was greater than 90 percent.

Source: University Hospital in Newark and Horizon Blue Cross Blue Shield of New Jersey announce value-based care collaborative. Horizon Blue Cross Blue Shield of New Jersey. News release. March 29, 2016.

Multiple Myeloma: A Rare Disease With a Major Economic Impact

Mona M. Chitre, PharmD, CGP, Vice President Pharmacy Management, Excellus BlueCross BlueShield; Joseph Mikhael, MD, MEd, FRCPC, FACP, Professor of Medicine, Mayo Clinic College of Medicine

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Multiple myeloma (MM) is a rare, progressive, and incurable form of cancer that creates a significant burden on the health care system.[1,2] It is the result of the malignant transformation of plasma cells in the bone marrow; these are typically found in the bone marrow and are responsible for making antibodies (immunoglobulins) to fight off infection. Cancerous plasma cells, the key myeloma cell, produce large quantities of abnormal immunoglobulin, which is monoclonal (often called the M protein) — in contrast to normal polyclonal immunoglobulin. This also leads to a decrease in the levels of functional immunoglobulins in affected patients. Furthermore, the proliferation of abnormal plasma cells in the marrow interferes with normal blood cell production. The etiology of this disease is not known, but it is more common in men and in the African-American population.

The hallmark of myeloma is the presence of end-organ damage known as CRAB — elevated calcium, renal insufficiency, anemia, and bone disease. These criteria have recently been updated to include three more criteria — greater than 60 percent plasmacytosis, immunoglobulin light chains involved/uninvolved over 100, and an MRI finding of greater than one focal lesion in the marrow.[3] Myeloma can exist in a "single" form, where only a small collection of plasma cells exist, known as a "solitary plasmacytoma," but this is a rare condition.

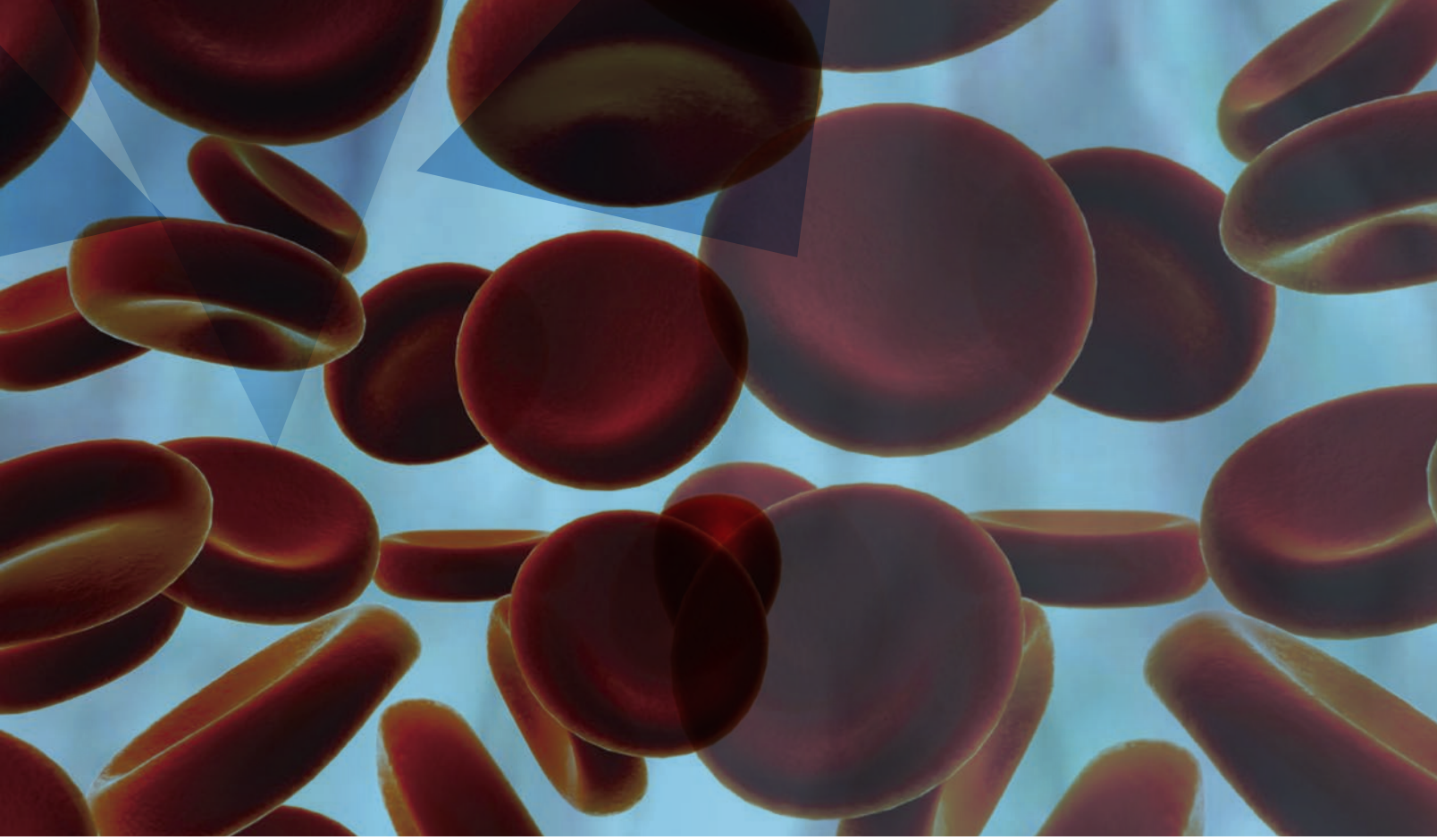
Multiple myeloma is a relatively rare cancer that accounts for only 10 percent of all blood cancers and 1.6 percent of all new cancers in the United States.[1] The American Cancer Society presents U.S. estimates for 2016 as follows:[4]

- About 30,330 new cases will be diagnosed (17,900 in men and 12,430 in women)
- About 12,650 deaths are expected to occur (6,430 in men and 6,220 in women)

The overall lifetime risk of getting MM is one in 143 (0.7 percent).[4] The mean age of affected patients is 62 years in men (75 percent > 70 years) and 61 years in women (79 percent > 70 years).[5] Thus, it is a disease of the elderly. The five-year survival rate increased from 25 percent in 1975 to 34 percent in 2003, according to the Surveillance, Epidemiology, and End Results (SEER) database, mainly due to newer and more effective treatment options.[5] In a review of newly diagnosed patients seen at the Mayo Clinic from 1971 to 2010, the median overall survival (OS) increased from 2.5 years in patients diagnosed before 2001 to 4.6 years in patients diagnosed from 2001 to 2005, and to 6.1 years in patients diagnosed from 2006 to 2010.[3] In this same review, the six-year OS in patients > 65 improved from 31 percent (2001–2005) to 56 percent (2006–2010).[3]

Diagnosis and Patient Identification

In order to diagnose a patient with MM, a complete diagnostic workup should be performed, including a history and physical examination, baseline blood studies, and biological assessments.[5] Until 2014, diagnosis was based strictly on clinicopathological criteria, which required evidence of specific end-organ damage caused by the underlying clonal plasma cell disorder. Hyper**C**alcemia,



Renal failure, **A**nemia, or **B**one lesions (CRAB features) were required to make a diagnosis of malignancy.[3] Patients not reaching end-organ damage were considered to have either monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM).[3] Table 1 discusses the updated diagnostic criteria set forth by the International Myeloma Working Group (IMWG) in order to earlier diagnose patients before the onset of end-organ damage. Other methods used in diagnosing MM include:[5]

- A 24-hour urinalysis to detect and evaluate the M protein
- Serum analysis to detect immunoglobulin levels
- Bone marrow aspiration and biopsy to detect specific chromosomal abnormalities
- Skeletal survey, MRI, CT, and/or PET scans

Patients with active myeloma are categorized by stage, using the International Staging System (ISS).[5] The ISS uses easily obtained lab measures and is easier to use than the previously used Durie-Salmon staging system for patients with previously untreated MM.[5] The ISS provides predictive information on overall prognosis. In 2015, the ISS was combined with chromosomal abnormalities (CA) detected by interphase fluorescent in situ hybridization (iFISH) and serum lactate dehydrogenase (LDH) to evaluate their prognostic value in newly diagnosed MM patients. The goal of the revised ISS (R-ISS) was to create a simple and easily applicable model that combines validated and reliable disease-related prognostic factors.[6] The R-ISS is defined as:

- Stage I: ISS stage I (serum ß2-microglobulin level < 3.5 mg/L and serum albumin level ≥ 3.5 g/dL) and standard-risk CA by iFISH and normal LDH
- Stage II: Not R-ISS stage I or II
- Stage III: SS stage III (serum ß2-microglobulin level > 5.5 mg/L) and either high-risk CA by iFISH or high LDH

The combination of three different prognostic tools in the R-ISS allows a better evaluation of patient prognosis; approximately 26 percent of patients would have been wrongly allocated to a good-prognosis group if only one of these three factors had been considered, and ultimately, a better definition of MM subgroups is essential to provide more effective personalized therapies.[6]

Therapy Options

Treatment for MM is determined based on whether the patient is eligible for stem cell transplantation as well as whether the patient is newly diagnosed or has had previous therapy. Treatment also includes adjunctive therapy.[5] If the patient is suitable for transplant, alkylator and nitrosourea therapy is usually not recommended or reduced in patients who may require autologous stem cell collection to avoid injury to the stem cells. A single autologous stem cell transplant (ASCT) has been associated with superior event-free survival compared with chemotherapy and is considered the preferred approach in newly diagnosed patients.[7] Typically, four cycles of induction chemotherapy followed by autologous stem cell support is widely used as the treatment in patients with MM. Transplant-eligible patients with active MM are treated with induction therapy and a combination of medications, usually based on bortezomib (Velcade®, Millennium), combined with cyclophosphamide (Cytoxan®,

Bristol-Myers Squibb), dexamethasone (Ozurdex®, Allergan), and Melphalan (Alkeran®, GlaxoSmithKline), although not used in induction, carfilzomib (Kyprolis®, Onyx), doxorubicin (Doxil®, Janssen), lenalidomide (Revlimid®, Celgene), or thalidomide (Thalomid®, Celgene), in either doublet or triplet regimens.[5,3] Once a certain depth of response is achieved, stem cells are harvested via apheresis, and the transplant is performed.[7] When relapse occurs after transplant, a second (tandem) ASCT may be considered for patients who relapse more than 12 to 18 months after the first transplant. Patients who relapse within 12 months of the initial transplant are best treated with agents they have not received before. For most patients, early ASCT after four cycles of initial therapy is preferred. However, randomized trials show that OS is similar whether ASCT is done immediately following four cycles (of induction therapy) or delayed (at the time of relapse as salvage therapy).[3] The timing and utilization of ASCT is an area of debate, and clinical trials continue to be done to answer these questions.

In patients who are not eligible for transplant, a combination of the medications listed above is used, determined by the category of their disease.[5] Melphalan is less likely to be used up front in light of the availability of novel agents. All treatments should be assessed after two cycles, and if there is evidence of response, ongoing therapy should be provided with bortezomib (Velcade), lenalidomide (Revlimid), or thalidomide (Thalomid), with or without a corticosteroid.[5]

Adjunctive therapy is also widely used and is very critical when treating MM. Conditions associated with MM, where adjunctive therapy is used, include bone disease, hypercalcemia, hyperviscosity, anemia, infection, and renal dysfunction, and are discussed further in Table 2.[5]

As in most other types of cancer, relapse is a major concern of MM patients and almost all patients will relapse at some point. The remission duration in relapsed MM decreases with each given regimen. The median progression-free survival (PFS) and OS in patients with relapsed MM refractory to lenalidomide (Revlimid) and bortezomib (Velcade) is poor, with median times of five months and nine months, respectively.[3] The most commonly used combinations for relapsed MM are similar to those used to treat newly diagnosed patients. If relapse occurs less than a year after stopping therapy, it is reasonable to administer the same therapy that was initially effective.[3] If patients are eligible for transplant or have already undergone a successful transplant, it is recommended they be considered for another as early as possible to reach optimal outcomes. It is important to act aggressively when dealing with relapse, and all relapse patients should be considered for clinical trial.[3]

There have been tremendous advances in the treatment of MM due to the recent availability of newer novel agents as well as the results of clinical trials. Table 3 displays some of the new approaches to treatment as well as associated costs that have been reported in these trials. Just in the past seven months three new agents — ixazomib (Ninlaro), elotuzumab (Empliciti), and daratumumab (Darzalex) — were approved for relapsed multiple myeloma. Indeed, there is an obvious trend to use more combination therapy in the relapse setting, often combining a proteasome inhibitor and immunomodulatory drug as opposed to simply using them sequentially.

Economic Impact

Health care resources are constantly being scrutinized and restrained, which makes it increasingly important to evaluate the economic impact associated with MM therapy and to understand the consequences of disease progression and treatment on the budget. Cancer treatment in the United States was estimated to cost $124.6 billion in 2010, and while MM accounts for only 1 percent of all patients with cancer, the associated costs over the course of the disease may be disproportionately high compared with other cancers. Due to an aging population, which encompasses an elongated patient survival due to improved therapies, these costs are projected to grow and are becoming increasingly important to patients, providers, and payors.[2] This presents a real problem for employers, patients, and payors as stakeholders in the market are challenged to provide affordable and appropriate care while optimizing affordable care. Multiple myeloma is considered a disease of the elderly, and older adults also tend to present with more comorbidities, adding to the cost of care. The growing number of elderly patients with cancer and chronic conditions is challenging because providers have to manage and assess the comorbidities when planning treatment, prescribing medications, and coordinating with the patient's primary care physician and/or additional specialists, making it imperative to assess practice needs.

In addition, the American Society of Clinical Oncology (ASCO) indicates that drug prices are unmanageable for payors, providers, and patients due to the increasing costs of therapies.[8] In a recent survey, 24 percent of Americans indicated they experience difficulty paying for prescription drugs, and 72 percent view the prices of prescription drugs as unreasonable.[8] Also, drug costs pose a challenge as Americans are claiming bankruptcy due to increasing oncology costs. Rising costs present barriers to care for the insured and uninsured, as the system continues to experience inconsistencies in care affecting patients all along the cancer continuum.[8]

While drug costs account for a large portion of medical costs associated with MM, medical costs due to complications that lead to hospitalizations is also a contributing factor to the incredible overall expense.[2] The Healthcare Cost and Utilization Project's National (Nationwide) Inpatient Sample determined a mean cost of $28,700 per patient per hospital stay (one of the highest among all cancers) and a cost of $522 million (based on 18,200 discharges) in 2009. They also found that the average length of stay of MM patients was longer than most other cancers and 28.4 percent of patients were readmitted within 30 days of discharge.[2] Costs associated with stem cell transplants and complications of the disease (bone disease, infection, anemia, renal failure) add to the economic burden of MM and also add to morbidity and mortality, thus increasing the burden to the patient and the health care system as a whole. Financial

and time constraints of caregivers, as well as the added administrative burdens to health care providers, must also be taken into account.[9]

In addition, the Institute of Clinical and Economic Review (ICER) released a draft guidance titled, "Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value."[10] However, providers and payors have had mixed reviews pertaining to this report; it is understood that the cost of care is rising, and the effort put into this report is appreciated. In order to create a report that can be digestible for payors and providers, the study tried to apply assumptions to distill information across several clinical trials. Unfortunately, some of the assumptions made led to shortcomings in the report. One of the assumptions was that, across triplet trials, the control arm was exactly the same; however, when one evaluates the studies, they are not the same. Negative costs were associated with adverse events, and then there were supportive care costs as well, but the report does not delineate what was evaluated in the adverse events or supportive care costs. In addition, the analysis was done on the four recently approved agents used in the treatment of multiple myeloma, and by ICER's own admission, there has been insufficient follow-up to accurately determine cost and value. However, many payors feel this is a step in the right direction in order to understand and obtain rational pricing, as well as trying to understand how to offset pricing. As per Table 4, the cost of multiple myeloma therapies has increased over the past two years.

Previous studies show that relapsed MM patients incur greater medical costs once they advance to later lines of therapy.[11] With the high costs of novel therapies putting a tremendous burden on limited health care budgets, it is increasingly important to determine whether new approaches to therapy can provide some relief to the overall costs of care. While clinical evidence has supported the use of novel agents along with increased treatment duration in newly diagnosed patients, there are questions about the economic impact of extending time to progression, along with the costs associated with relapse and these patients moving to a second line of therapy.[11] Monthly total direct costs for newly diagnosed patients were $15,400 in the first three months of treatment and declined each quarter, reaching approximately $5,000 per month at 18-plus months. At relapse, monthly costs increased to more than $12,000 for the first three months and followed a quarterly pattern of reduction similar to that seen for newly diagnosed patients.[12] In a study performed by Arikian et al., it was determined that with patients receiving a lenalidomide (Revlimid) or bortezomib (Velcade) based treatment, followed until time to next therapy, the total direct monthly costs per patient declined steadily over time, decreasing by 68 percent from the initial quarter to the period post-18 months. The results suggest that extending time to progression may provide an economic benefit for each month extended before relapse.[12] The total direct monthly costs attributed to these patients ranged from $8,942 to $11,139 for the lenalidomide (Revlimid) and bortezomib (Velcade) groups, respectively. While the overall drug costs associated with the two groups are similar, the lower overall medical costs in the lenalidomide (Revlimid) group may show that more effective drug therapy leads to a lesser impact on the budget.[12]

Managed Care Implications

As a result of the rising costs associated with cancer treatments, new payment and care models are under evaluation; in January 2015, Health and Human Services Secretary Sylvia M. Burwell announced a goal of combining 40 percent of Medicare payments with alternative payment models toward the end of 2016, and extending the proportion to 50 percent by 2018.[8] Examples of alternative payment models include:

Accountable Care Organizations (ACOs) ASCO introduced the Patient-Centered Oncology Payment (PCOP) model in March 2015. The PCOP model incorporates increased and flexible payments for treatment planning, care management, and accountability, when delivering high-quality care. The PCOP model introduces four new payments for specific clinical services, in addition to the existing services that providers bill to payors. These include new patient treatment planning, care management during treatment, care management during active monitoring after treatment, and participation in clinical trials. The PCOP model is different from the shared savings payments because individual providers are not required to reduce spending to receive these additional payments. However, in exchange for these new payments, practices are responsible for providing high-quality care through four of the following measures:

- Reducing emergency department visits and hospital admissions that result from treatment complications
- Following evidence-based guidelines and using lower-cost alternatives where they have shown to be equivalent to higher-cost options
- Providing high-quality end-of-life care
- Providing care consistent with ASCO quality standards

Bundled Payments or Episodes of Care Some payors have started alternative payment projects for cancer care, some of which have been implemented in conjunction with large oncology centers. For example, some payors have developed episode-based payments for some services; a report highlighted that after a year of implementation, physician compliance with recommended treatments improved, and there were cost savings associated with reduced administrative needs, and improved patient satisfaction.

Clinical Pathways In 2016, ASCO issued recommendations to improve the development of oncology pathways and processes, showing the demonstration of a pathway that promotes evidence-based, high-value care.

Patient-Centered Medical Homes (PCMH) Private and public payors have started to evaluate the use of PCMHs in cancer care. Standards address multiple facets of care, which includes the coordination of referrals, access and

Table 1: IMWG Diagnosing Criteria for MM and Other Plasma Cell Disorders[3]

Disorder	Disease Definitions
Monoclonal gammopathy of undetermined significance (MGUS)	All three criteria must be met: • Serum monoclonal protein (non-IgM type) < 3 g/dL • Clonal bone marrow plasma cells < 10% • Absence of end-organ damage (such as CRAB) that can be attributed to the plasma cell proliferative disorder
Smoldering MM	Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL, or urinary monoclonal protein ≥ 500 mg per 24h and/or clonal bone marrow plasma cells 10% to 60% • Absence of myeloma defining events or amyloidosis

MM	Both criteria must be met:
	• Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma
	• One or more of the following MM defining events:
	  • Evidence of end-organ damage
	  • Clonal bone marrow plasma cell percentage ≥ 60%
	  • Involved: uninvolved serum free light chain (FLC) ratio ≥ 100 (involved FLC level must be ≥ 100 mg/L)

IgM monoclonal gammopathy of undetermined significance (IgM MGUS)	All three criteria must be met: • Serum IgM monoclonal protein < 3 g/dL • Bone marrow lymphoplasmacytic infiltration < 10% • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder
Light chain MGUS	All criteria must be met: • Abnormal FLC ratio (< 0.26 or > 1.65) • Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26) • No immunoglobulin heavy chain expression on immunofixation • Absence of end-organ damage that can be attributed to plasma cell proliferative disorder • Clonal bone marrow plasma cells < 10% • Urinary monoclonal protein < 500 mg/24h

communication, planning and managing care, shared decision-making, tracking and coordination of care and testing, and measurement and improvement of performance.

As the population continues to age, and with budgets constantly being scrutinized and evaluated, there is an ever-growing need to find ways to provide health care as cost-effectively as possible. New approaches to care, including improved imaging, genetic testing, biomarkers, and patient-specific targeted therapies are all ways to help mitigate expenditure.[13] An analysis of every aspect of MM care can demonstrate that the less costly therapies may not always provide the best possible health outcomes or the most cost benefit.[9] Drug therapy, while accounting for a large percentage of costs, should not be the only consideration when determining the most appropriate treatment. One cost-savings approach that has been deemed successful is the implementation of a medical home concept, where an oncologist-led team of nurses, pharmacists, case managers, and other administrative staff collaborate in the care of the patient.[13] Payors continue to consider not only the economic factors, but also quality of life and pharmacoeconomic analyses to determine the most cost-effective therapies, and a partnership between patients, caregivers, and payors will help ensure access to therapies that will produce the most beneficial results for both patients and payors. Although containing costs is imperative in any health care system, quality of care and affordability continues to remain a priority of the current health care system.

Table 2: Adjunctive Treatment[5]

Disorder	Treatment
Bone disease	• All patients receiving MM therapy should be given bisphosphonates (pamidronate [Aredia®]) or (zoledronic acid [ZOMETA®]) – Prior dental exam recommended • Smoldering or stage I patients (preferably in clinical trial) should have annual bone survey or if symptomatic • Monitor for renal dysfunction • Monitor for osteonecrosis of jaw (ONJ) • Orthopedic consultation for impending or actual long-bone fracture or bony compression of spinal cord, or vertebral column instability
Hypercalcemia	• Hydration/furosemide (Lasix®), bisphosphonates, steroids, and/or calcitonin (Calcitriol®)
Hyperviscosity	• Plasmapheresis should be used if symptomatic
Anemia	• Consider erythropoietin for anemic patients
Infection	• IVIG (intravenous Immunoglobulin) therapy • Consider pneumococcal and influenza vaccine • PCP (pneumocystis carinii pneumonia), herpes, and antifungal prophylaxis if on high-dose dexamethasone (Maxidex®) regimen • Herpes zoster prophylaxis if treated with a proteasome inhibitor such as bortezomib (Velcade), carfilzomib (Kyprolis), or ixazomib (Ninlaro)
Renal dysfunction	• Maintain hydration • Avoid NSAIDs • Plasmapheresis • Hemodialysis
Coagulation/thrombosis	• Prophylactic anticoagulation therapy recommended for thalidomide (Thalomid) based or lenalidomide (Revlimid) with dexamethasone (Maxidex) therapy

Table 3: Combination Therapy Regimens and Associated Costs (Annual Cost per Patient)[2,5]

Regimen	Commercial		Medicare	
	Pharmacy Benefit ($)	Medical Benefit ($)	Pharmacy Benefit ($)	Medical Benefit ($)
Bortezomib (Velcade) + dexamethasone (Ozurdex)	6	79,988	6	64,768
Lenalidomide (Revlimid) + dexamethasone	117,069	0	117,069	0
Panobinostat (Farydak®) + bortezomib + dexamethasone	50,704	55,805	50,704	45,187
lenalidomide, bortezomib, dexamethasone	97,554	85,568	97,554	69,286
Carfilzomib (Kyprolis), lenalidomide, dexamethasone	100,811	148,326	100,811	120,102
Carfilzomib	0	136,878	0	110,833
Pomalidomide (Pomalyst®) + dexamethasone	135,774	0	135,774	0
Total	501,918	506,565	501,918	410,176

Table 4: AWP* Unit Pricing[14]

Drug	Year 2015	Year 2016	Percent Change from 2015-2016
Revlimid 5 mg	$603.23	$644.25	6.8%
Velcade 3.5 mg	$1,932.00	$1,943.40	0.1%
Kyprolis 60 mg	$2,234.34	$2,299.14	2.9%
Ninlaro 2.3 mg	-	$3,468.00	-
Farydak 15 mg	$1,372.00	$1,466.67	6.9%
Pomalyst 3 mg	$698.66	$746.17	6.8%
Empliciti	$2,131.20	-	-

**Average Wholesale Price*
Source: Micromedex – Red Book Online

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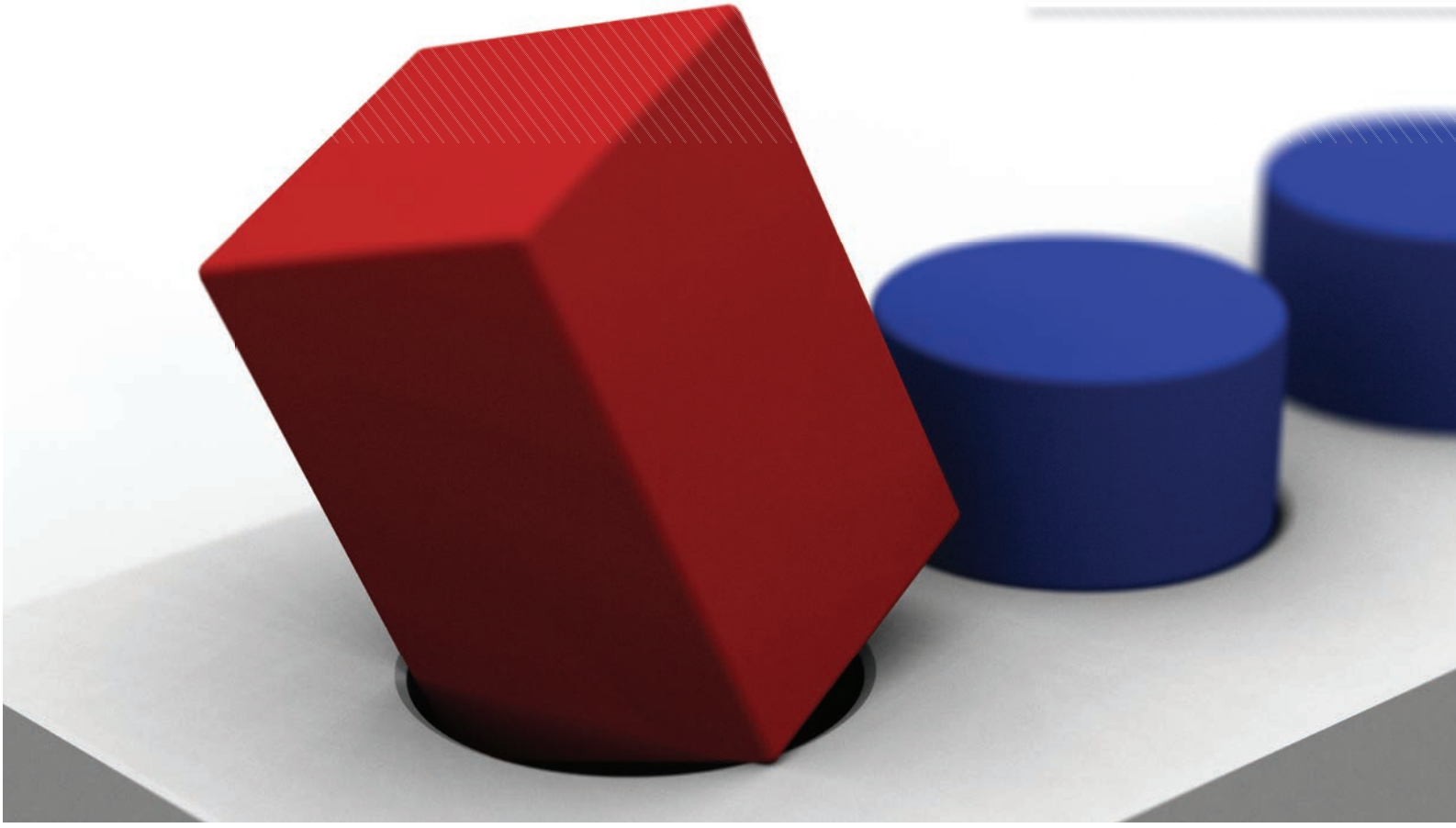

ViiV Healthcare

The first and only oral proteasome inhibitor

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EXTEND EFFICACY.
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- The approval of the NINLARO® (ixazomib) regimen (NINLARO+lenalidomide+dexamethasone) was based on a **statistically significant ~6 month improvement in median PFS vs the placebo regimen (placebo+lenalidomide+dexamethasone)**
  - Median PFS: 20.6 vs 14.7 months (95% CI, 17.0-NE and 95% CI, 12.9-17.6, respectively; HR=0.74 [95% CI, 0.587-0.939]; *P*=0.012)

NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

IMPORTANT SAFETY INFORMATION FOR NINLARO

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia** has been reported with NINLARO. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines. Adjust dosing as needed. Platelet nadirs occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle.
- **Gastrointestinal Toxicities**, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.

NE=not evaluable; PFS=progression-free survival.

Please see next page for additional Important Safety Information and Brief Summary on subsequent pages.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend ixazomib as a category 1 treatment option for previously treated multiple myeloma.[1]

NINLARO® (ixazomib) capsules
4mg | 3mg | 2.3mg

WARNINGS AND PRECAUTIONS (continued)

- **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO® (ixazomib). The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.
- **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.
- **Cutaneous Reactions:** Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification.
- **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.
- **Embryo-fetal Toxicity:** NINLARO can cause fetal harm. Women should be advised of the potential risk to a fetus, to avoid becoming pregnant, and to use contraception during treatment and for an additional 90 days after the final dose of NINLARO.

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%).

SPECIAL POPULATIONS

- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.
- **Lactation:** Advise women to discontinue nursing while on NINLARO.

DRUG INTERACTIONS: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

Please see adjacent Brief Summary.

TOURMALINE-MM1: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of NINLARO (an oral proteasome inhibitor) vs placebo, both in combination with lenalidomide and dexamethasone, until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received at least 1 prior therapy.

USO/IXA/16/0099(1)

REFERENCE: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.3.2016. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed April 5, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

NINLARO® (ixazomib) capsules
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BRIEF SUMMARY OF PRESCRIBING INFORMATION
NINLARO (ixazomib) capsules, for oral use

1 INDICATION

NINLARO (ixazomib) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Three percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤ 10,000/mm^3 during treatment. Less than 1% of patients in both regimens had a platelet count ≤ 5000/mm^3 during treatment. Discontinuations due to thrombocytopenia were similar in both regimens (< 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen discontinued one or more of the three drugs). The rate of platelet transfusions was 6% in the NINLARO regimen and 5% in the placebo regimen.

Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.2 Gastrointestinal Toxicities: Diarrhea, constipation, nausea, and vomiting, have been reported with NINLARO, occasionally requiring use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 42% of patients in the NINLARO regimen and 36% in the placebo regimen, constipation in 34% and 25%, respectively, nausea in 26% and 21%, respectively, and vomiting in 22% and 11%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

5.3 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (8% in the NINLARO regimen and 5% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens; there were no Grade 4 or serious adverse reactions.

The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

5.4 Peripheral Edema: Peripheral edema was reported in 25% and 18% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (16% in the NINLARO regimen and 13% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 4% in the placebo regimen).

Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. There was no Grade 4 peripheral edema reported. There were no discontinuations reported due to peripheral edema. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

5.5 Cutaneous Reactions: Rash was reported in 19% of patients in the NINLARO regimen and 11% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (10% in the NINLARO regimen and 7% in the placebo regimen) or Grade 2 (6% in the NINLARO regimen and 3% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 1% of patients in the placebo regimen. There were no Grade 4 or serious adverse reactions of rash reported. The most common type of rash reported in both regimens included maculo-papular and macular rash. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.

5.6 Hepatotoxicity: Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

5.7 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using NINLARO. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with NINLARO. If NINLARO is used during pregnancy or if the patient becomes pregnant while taking NINLARO, the patient should be apprised of the potential hazard to the fetus. Advise females of reproductive potential that they must use effective contraception during treatment with NINLARO and for 90 days following the final dose.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other sections of the prescribing information:

- Thrombocytopenia [*see Warnings and Precautions (5.1)*]
- Gastrointestinal Toxicities [*see Warnings and Precautions (5.2)*]
- Peripheral Neuropathy [*see Warnings and Precautions (5.3)*]
- Peripheral Edema [*see Warnings and Precautions (5.4)*]
- Cutaneous Reactions [*see Warnings and Precautions (5.5)*]
- Hepatotoxicity [*see Warnings and Precautions (5.6)*]

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

The safety population from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=360) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=360).

The most frequently reported adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO regimen.

Table 4: Non-Hematologic Adverse Reactions Occurring in ≥ 5% of Patients with a ≥ 5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

	NINLARO + Lenalidomide and Dexamethasone N=360			Placebo + Lenalidomide and Dexamethasone N=360		
System Organ Class / Preferred Term	**N (%)**			**N (%)**		
	All	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**
Infections and infestations						
Upper respiratory tract infection	69 (19)	1 (< 1)	0	52 (14)	2 (< 1)	0
Nervous system disorders						
Peripheral neuropathies*	100 (28)	7 (2)	0	77 (21)	7 (2)	0
Gastrointestinal disorders						
Diarrhea	151 (42)	22 (6)	0	130 (36)	8 (2)	0
Constipation	122 (34)	1 (< 1)	0	90 (25)	1 (< 1)	0
Nausea	92 (26)	6 (2)	0	74 (21)	0	0
Vomiting	79 (22)	4 (1)	0	38 (11)	2 (< 1)	0
Skin and subcutaneous tissue disorders						
Rash*	68 (19)	9 (3)	0	38 (11)	5 (1)	0
Musculoskeletal and connective tissue disorders						
Back pain	74 (21)	2 (< 1)	0	57 (16)	9 (3)	0
General disorders and administration site conditions						
Edema peripheral	91 (25)	8 (2)	0	66 (18)	4 (1)	0

Note: Adverse reactions included as preferred terms are based on MedDRA version 16.0.

*Represents a pooling of preferred terms

(Continued on next page)

Table 5: Thrombocytopenia and Neutropenia (pooled adverse event and laboratory data)

	NINLARO + Lenalidomide and Dexamethasone N=360		Placebo + Lenalidomide and Dexamethasone N=360	
	N (%)		N (%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Thrombocytopenia	281 (78)	93 (26)	196 (54)	39 (11)
Neutropenia	240 (67)	93 (26)	239 (66)	107 (30)

Eye Disorders

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 26% in patients in the NINLARO regimen and 16% of patients in the placebo regimen. The most common adverse reactions were blurred vision (6% in the NINLARO regimen and 3% in the placebo regimen), dry eye (5% in the NINLARO regimen and 1% in the placebo regimen), and conjunctivitis (6% in the NINLARO regimen and 1% in the placebo regimen). Grade 3 adverse reactions were reported in 2% of patients in the NINLARO regimen and 1% in the placebo regimen.

The following serious adverse reactions have each been reported at a frequency of < 1%: acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

7 DRUG INTERACTIONS

7.1 Strong CYP3A Inducers: Avoid concomitant administration of NINLARO with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Women should avoid becoming pregnant while being treated with NINLARO.

Risk Summary: NINLARO can cause fetal harm when administered to a pregnant woman. There are no human data available regarding the potential effect of NINLARO on pregnancy or development of the embryo or fetus. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with NINLARO. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. *Animal Data:* In an embryo-fetal development study in pregnant rabbits there were increases in fetal skeletal variations/abnormalities (caudal vertebrae, number of lumbar vertebrae, and full supernumerary ribs) at doses that were also maternally toxic (≥ 0.3 mg/kg). Exposures in the rabbit at 0.3 mg/kg were 1.9 times the clinical time averaged exposures at the recommended dose of 4 mg. In a rat dose range-finding embryo-fetal development study, at doses that were maternally toxic, there were decreases in fetal weights, a trend towards decreased fetal viability, and increased post-implantation losses at 0.6 mg/kg. Exposures in rats at the dose of 0.6 mg/kg was 2.5 times the clinical time averaged exposures at the recommended dose of 4 mg.

8.2 Lactation: It is not known whether NINLARO or its metabolites are present in human milk. Many drugs are present in human milk and as a result, there could be a potential for adverse events in nursing infants. Advise women to discontinue nursing.

8.3 Females and Males of Reproductive Potential: *Contraception* - Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment. *Infertility* - Fertility studies were not conducted with NINLARO; however there were no effects on reproductive organs in either males or females in nonclinical studies in rats and dogs

8.4 Pediatric Use: Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. 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 patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment: In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

8.7 Renal Impairment: In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis.

10 OVERDOSAGE: There is no known specific antidote for NINLARO overdose. In the event of an overdose, monitor the patient for adverse reactions and provide appropriate supportive care.

17 PATIENT COUNSELING INFORMATION

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

Dosing Instructions

- Instruct patients to take NINLARO exactly as prescribed.
- Advise patients to take NINLARO once a week on the same day and at approximately the same time for the first three weeks of a four week cycle.
- Advise patients to take NINLARO at least one hour before or at least two hours after food.
- Advise patients that NINLARO and dexamethasone should not be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
- Advise patients to swallow the capsule whole with water. The capsule should not be crushed, chewed or opened.
- Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
- If a patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is ≥ 72 hours away. Advise patients not to take a missed dose if it is within 72 hours of their next scheduled dose.
- If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
- Advise patients to store capsules in original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO.

Thrombocytopenia: Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising.

Gastrointestinal Toxicities: Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their physician if these adverse reactions persist.

Peripheral Neuropathy: Advise patients to contact their physicians if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs.

Peripheral Edema: Advise patients to contact their physicians if they experience unusual swelling of their extremities or weight gain due to swelling.

Cutaneous Reactions: Advise patients to contact their physicians if they experience new or worsening rash.

Hepatotoxicity: Advise patients to contact their physicians if they experience jaundice or right upper quadrant abdominal pain.

Pregnancy: Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with NINLARO and for 90 days following the final dose. Advise patients to contact their physicians immediately if they or their female partner become pregnant during treatment or within 90 days of the final dose.

Concomitant Medications: Advise patients to speak with their physicians about any other medication they are currently taking and before starting any new medications.

Please see full Prescribing Information for NINLARO at NINLARO-hcp.com.

20160209 v2 USO/IXA/15/0123(2)

Medical Drug Management Strategies

Saira A. Jan, MS, PharmD, Director of Pharmacy Strategy and Clinical Integration, Horizon Blue Cross Blue Shield of New Jersey

The rising cost of prescription drugs is one of the many challenges facing the health care industry and is prompting payors to explore opportunities to effectively manage health care costs. In 2014, the total drug spending in the United States was $373.9 billion; of this, $124 billion was spent on specialty drugs.[1] However, it is estimated that 50 percent of specialty drug costs are billed through the medical benefit and therefore, the true cost of specialty medication is likely to be much higher.[2] Continued growth in specialty spending through the medical benefit is expected due to a variety of factors, including the following:

- Over the past decade, the late-stage research and development pipeline has shifted to include 42 percent of specialty medicines.
- Legislation is driving a surge in orphan drug research and launches.
- FDA incentive programs and expedited approval pathways are accelerating specialty drug development efforts.[1]

Historically, medical drug management has not been as successful as pharmacy drug management. However, increasing health care costs, the expense associated with specialty drug utilization, and the growth in drug spending through the medical benefit will drive payor efforts to develop and implement strategies for managing medical drug costs. A key aspect of this will be a heightened focus on evaluating, and developing or enhancing medical formularies as a strategy for medical drug management.

Current Landscape, Opportunities, and Challenges

As analysts report a substantial amount of wasteful spending is driven by the lack of coordination of care and services, the health care system is increasingly focused on care coordination.[3] Disparities in the management of drugs covered under the medical drug benefit and those administered under the pharmacy benefit offer a prime opportunity for implementing medical drug management strategies as a means of improving communication and cutting costs on drug expenditures that have not historically received the attention given to pharmacy costs.[4] A high level overview of the management of drug spending suggests there are several factors that contribute to key differences in drug management strategies, including:

- System design
- Processes
- Capabilities
- Resources

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Historically, drug management systems have focused on the oversight of the traditional pharmacy benefit. Payors and other stakeholders have developed processes aligned with this philosophy. Efforts have focused on managing product selection, coverage and reimbursement, and aligning the financial interests of payors, pharmacies, pharmaceutical manufacturers, and patients. In the current pharmacy benefit system, access to prescription drugs is managed through "traditional" benefit and formulary design strategies. These systems support payors in implementing programs that establish a framework for pharmacy management. This level of influence does not, however, exist within the currently defined and implemented medical drug benefit system and oversight process.

Payors focusing on making the changes necessary to effectively manage medical drug spending will be challenged to consider current systems and processes, as well as the capabilities and resources necessary. Effective programs will require coordination, oversight, and revisions of existing management strategies. Assessment of the internal capabilities to implement and expand medical drug management programs — including the capacity to coordinate these efforts with all stakeholders — is essential. Finally, payors must determine that there are sufficient resources allocated to these programs, as demand for these programs will likely expand. Benefit from these efforts is anticipated, as it's estimated that due to the absence of clinical policies or a lack of strategies as reasoning for their enforcement. These may include the implementation of a prior authorization

process, since about 15 to 20 percent of medical benefit drug requests do not meet evidence-based treatment guidelines, and therefore do not meet criteria necessary to warrant coverage by health plans. Managing these treatments could translate into an estimated $1.3 billion in annual savings, simply by ensuring treatment is appropriate.[5]

Benefit Design

The first step in developing a medical pharmacy benefit strategy should be the development of a cross-benefit design strategy. This is crucial since medical drug management strategies offer payors both an opportunity and a challenge. Drug-specific strategies require alignment of the medical and pharmacy benefit criteria. This coordination was identified as a challenge by 60 percent of representatives of the 70 commercial health plans participating in the EMD Serono Specialty Digest Survey.[6]

Payors must give thoughtful consideration to overall benefit design as any efforts must be coordinated and consistent with overall organizational goals and objectives. Prior to program development, payors must assess the current benefit design and determine the appropriate benefit placement for therapies, i.e., coverage under the medical benefit, pharmacy benefit, or both. This is not to imply payors should avoid covering treatments under the medical benefit. Rather, placement should consider clinical and economic factors. Many specialty medications require involvement of health care professionals for administration, monitoring, dose titration, and management of side effects in order to optimize clinical outcomes. These therapies often lend themselves to coverage under the medical benefit, while patient self-administered specialty therapies commonly lend themselves to coverage under the pharmacy benefit.

Ideally, medical pharmacy management strategies should be identified for key drugs or treatment categories. Usually these are specialty drugs processed under the medical benefit, for treatment of high-cost conditions, with a strong likelihood for successful management with the implementation of medical pharmacy management strategies. These are predominantly drugs administered by a health care provider, usually within a "high touch" service model such as home infusion, physician offices, infusion centers, or inpatient settings.[7, 8]

Selection of Medical Formulary Management Products

Successful medical pharmacy management requires payors to first identify therapeutic categories for inclusion in the medical formulary. Each drug in a given category is then evaluated from both a clinical and financial perspective. Products are clinically differentiated based on efficacy, safety, treatment location (e.g., hospital inpatient, infusion center, emergency room, etc.) and convenience. A full therapeutic class review should be done, including an assessment of indications, side effect profile, unique product attributes, benefits, risks, inclusion in evidence-based guidelines, and evidence from clinical trials. When multiple products are considered interchangeable or clinically equivalent, then financial analyses are completed to determine the cost per treatment course. These assessments should consider the cost of the medication as well as the total cost of treatment and management associated with a therapy. This may include administration costs, laboratory and monitoring, and related expenses.

Once completed, the costs associated with treatments are evaluated and payors consider additional factors such as market share and rebate contracts. All of this information is integrated — allowing payors to develop a full picture of the treatment options within a therapeutic class. Innovative programs are emerging in various geographies that consider all aspects of care comprehensively, but in light of the unique attributes of each area, such as New Jersey's Organized Systems of Care initiative. With this as background, foundational research and product preferencing efforts begin. Decisions should be based on the product with the highest value — with value defined by considering efficacy, safety, breadth of indications, expense associated with monitoring and administration, cost of therapy, and rebates. The top categories for medical benefit drug spending for commercial plans in 2014 are listed in Figure 1 by per member per month (PMPM), cost per patient.

Clearly, such a thorough evaluation requires collaboration and input from key decision-makers, pharmacy and therapeutics committees, relevant medical committees, physician specialists, or other key stakeholders with insight regarding a particular disease state or treatment. Once consensus is reached regarding key target categories for payor development of medical drug management policies, then evidence-based, medical prior authorization criteria should be developed, implemented, and enforced.

Management Strategies

Drugs billed under the medical benefit do not fall within the scope of traditional pharmacy benefit management (PBM) strategies. These therapies are increasingly on payors' radar, and the management opportunities are significant. Medical pharmacy management strategies may be viewed from the perspective of developing and implementing strategies that fall into the following broad categories: [5, 9]

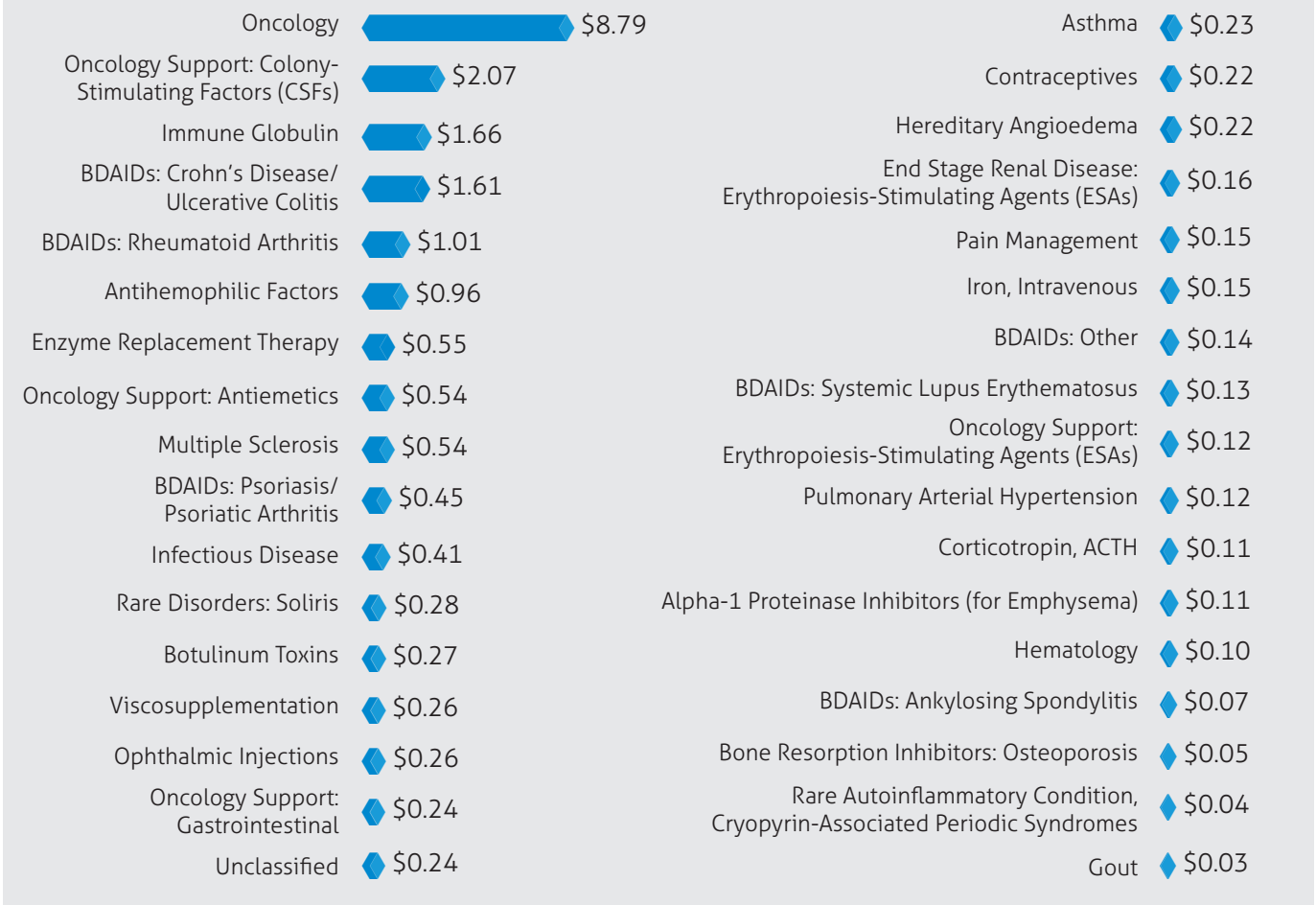
- Utilization Management
- Site of Care (SOC) Management
- Payment Management

A robust medical formulary management strategy serves as the cornerstone for an effective medical drug management program.

Utilization Management: Payors most frequently report efforts centered on utilization management strategies, such as those included in the traditional pharmacy formulary management process. These strategies often center on product preferencing, the selection of specific preferred drugs for a category that is processed through the medical benefit, similar to pharmacy benefit management product preferencing. An estimated 92 percent of payors report product preferencing for at least some medical pharmacy therapies, and Figure 2 describes therapeutic classes within which payors report having product preferencing in place. Product preferencing objectives are typically supported by utilizing prior authorization processes, step therapy requirements, clinical pathways, differential physician reimbursement strategies, benefit design, and post-service claim edits. Table 1 demonstrates the utilization management tools payors report utilizing by disease state or drug category and may include, in addition to the previously discussed strategies, clinical pathways, and postservice claim edits systems, discussed later. These methods for effective utilization management strategies are applied to govern the use of concomitant therapies, indications for use, duration of therapy, frequency of administration, and dose as demonstrated in Figure 3.

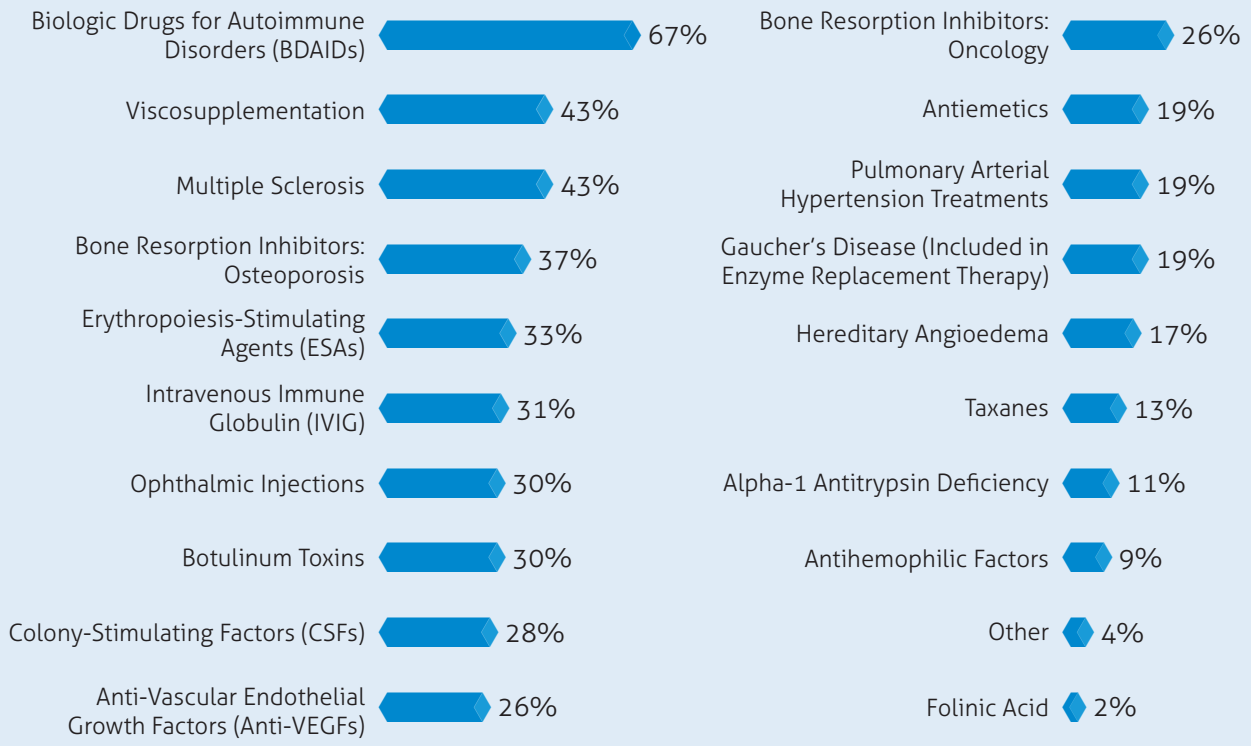
Utilization management strategies related to medical pharmacy formulary oversight may grow increasingly sophisticated as supported by technological advances. For example, payors may develop criteria for increasingly precise management of costly therapies. Use of genetic testing might be a means of managing use of some therapies; but must be accompanied by the corresponding assessment of the cost of testing, compared with its accuracy and value in informing

Figure 1: 2014* Commercial PMPM by Disease State or Drug Category[2]



*Most recent year for which data is available.

Figure 2: 2015 Medical Benefit Disease State or Drug Category With Product Preferencing Currently in Place[2] *% Payors, n=54 payors, 98 million covered lives*



treatment decisions. Payors must proceed with caution in weighing the benefits of testing in improving selection of therapy and clinical outcomes, compared with the cost of indiscriminate testing that provides little to no clinical value.[10-12]

Site of Care Management: It is important to touch upon the potential value of managing the site of care as a means of controlling costs associated with drugs processed under the medical benefit. Typically, therapies administered at a physician's office or in the patient's home are usually less costly than having the same treatment given in a hospital infusion facility. This is often due to contract configurations and the billing of these therapies as a percentage of billed charges. Additional strategies may include recontracting to establish drug price benchmarks or moving medications from the medical to the pharmacy benefit when clinically appropriate, but these strategies may be part of a long-term process and are not always feasible. It's estimated that site of care programs, if implemented nationally by U.S. payors to direct treatment to the most clinically appropriate and lowest cost channel, could yield savings of up to $1.7 billion annually.[5] In order to be of value, a site of care management program must align with formulary product preferencing, as well as reimbursement strategies. Done correctly, it is possible to implement strategies for managing the sites of service for medical benefit drugs.

Payment/Financial Management: Opportunities exist for most payors to refine payment management systems in order to reduce overpayments, and maximize the opportunity to capture rebates for which they qualify. This is a management opportunity since drugs paid for under the medical benefit may be billed by various means, including the Healthcare Common Procedure Coding System (HCPCS) units, National Drug Code (NDC) units, or by dosage, unit of use, etc. This differs from the pharmacy benefit, whereby specialty drugs are benchmarked according to the NDC code. Several strategies may be employed that can benefit payors in terms of payment management.

Postservice Claim Edits: For drugs that do not require a prior authorization, payors report using postservice, prepayment claim edits to assess claims for:

- Appropriate doses based on fixed dosing regimens
- Appropriate indications
- Appropriate doses based on weight-based dosing regimens
- Appropriate frequency
- Maximum cost thresholds
- Accuracy of applying correct contracted rates to claims

It's estimated that claims management tools could save payors as much as $1.9 billion annually.[5] A robust claim review and edit program could support medical pharmacy management efforts by enhancing data available to help payors qualify for and receive rebates for drugs dispensed under the medical benefit.

Table 1: 2015 Utilization Management Tools for Medical Benefit Drugs by Disease State or Drug Category[2] *% Payors, n=59 payors, 130 million covered lives*

Disease State or Drug Category	Care Management (e.g., Disease Management or Case Management)	Prior Authorization	Step Edit Requirements	Clinical Pathways	Post-Service Claim Edits	None	Total Average Management
Biologic Drugs for Autoimmune Disorders (BDAIDs)	29%	88%	49%	0%	2%	3%	29%
Oncology	46%	78%	10%	19%	2%	2%	26%
Erythropoiesis-Stimulating Agents (ESAs)	31%	76%	20%	19%	2%	2%	25%
Multiple Sclerosis	19%	100%	25%	2%	2%	0%	25%
Viscosupplementation	17%	78%	32%	10%	3%	3%	24%
Antihemophilic Factors	42%	64%	0%	10%	8%	17%	24%
Intravenous Immune Globulin (IVIG)	39%	88%	0%	8%	3%	0%	23%
Hereditary Angioedema	32%	76%	12%	0%	0%	12%	22%
Asthma	32%	95%	3%	0%	2%	0%	22%
Bone Resorption Inhibitors: Osteoporosis	20%	76%	19%	12%	2%	2%	22%
Colony-Stimulating Factors (CSFs)	29%	66%	7%	19%	2%	3%	21%
Alpha-1 Antitrypsin Deficiency	27%	73%	15%	7%	2%	0%	21%
Pulmonary Arterial Hypertension	32%	78%	2%	7%	2%	2%	20%
Antiemetics	22%	49%	0%	15%	2%	32%	20%
Respiratory Syncytial Virus (RSV) Prevention	24%	88%	0%	0%	5%	0%	19%
Bone Resorption Inhibitors: Oncology	19%	76%	3%	2%	2%	10%	19%
Enzyme Replacement Therapy	34%	69%	0%	0%	0%	2%	18%
Ophthalmic Injections	0%	66%	5%	7%	2%	5%	14%
Botulinum Toxins	0%	85%	2%	5%	2%	29%	16%
Total Average	**26%**	**77%**	**11%**	**7%**	**2%**	**5%**	**21%**

Figure 3: Medical Benefit Drug Prior Authorization Review Criteria 2014–2015[2]

% Lives, n=41 payors, 120 million lives (2014); n=59 payors, 130 million lives (2015)

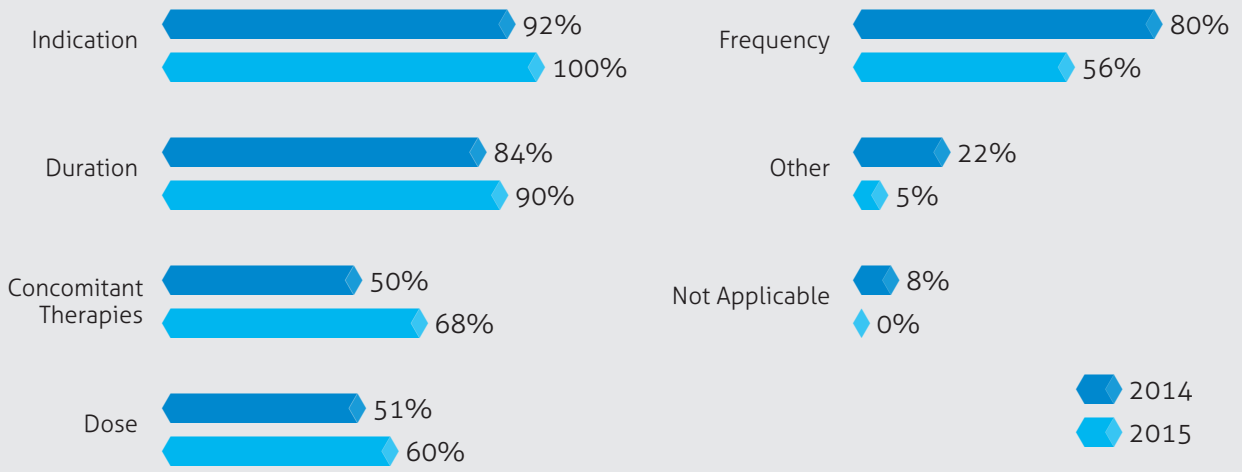
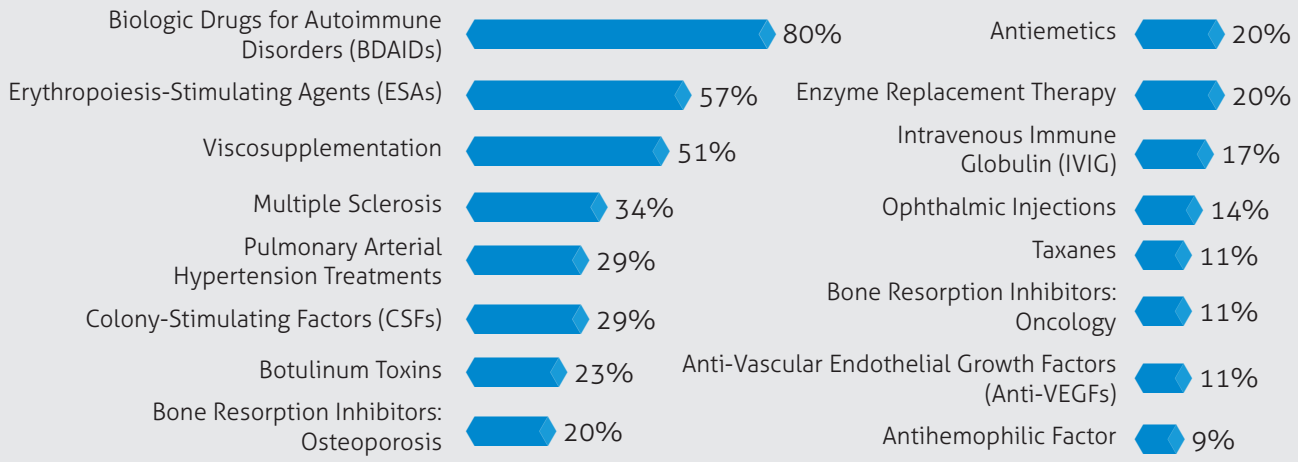


Figure 4: 2015 Disease State or Drug Category Where Payors Received Rebates for Medical Benefit Drugs[2] *% Payors, n=35 payors, 74 million covered lives*



Rebate Capture Strategies: Currently, plans representing about half of covered lives report receiving rebates on medical benefit drugs. Figure 4 shows the therapeutic classes where payors report receiving rebates for medical benefit drugs, and demonstrates significant opportunities for payors to realize savings. Clearly, payor rebate strategies are not "stand alone" and must align with provider reimbursement strategies as well as with the formulary. As part of the effort to align and maximize rebates, payors may consider creating formulary tiers for medical benefit administered therapies, similar to those employed in pharmacy benefit management programs. These are part of the potential that exists for creating management opportunities and capturing significant savings with a well thought out approach to medical pharmacy management.

Contracting Strategies: While a detailed discussion of contracting methodologies remains beyond the scope of this article, it must be mentioned that payors and pharmaceutical manufacturers are increasingly exploring outcomes-based contracting options. These agreements must be customized and data driven. Some drugs and disease states will more easily lend themselves to outcomes-based contracting, but interest and exploration of innovative strategies for contracting is growing.

Tiered Reimbursement Strategies: In support of product preference decisions, payors should consider developing a tiered reimbursement structure. Effectively designed, this can drive utilization of select or preferenced therapies, potentially

helping payors to capture rebates and perhaps support the use of cost-effective sites of care.[2]

To highlight the attributes of such a strategy, payors may stratify drugs into multiple reimbursement tiers. The first category of drugs would likely be moderately priced, multi-source therapies with significant AWP/ASP differentials, and would be covered at the highest ASP percentage level. The second group of drugs, likely newer, higher cost per claim single-source agents, like high-cost oncology or other injectable therapies, would net providers reimbursement at a lower ASP percentage. Meanwhile, a third category of therapies may be comprised of maximum allowable cost (MAC) or least cost alternative (LCA) therapies. Drugs included in this grouping are likely to be generics or injectables in classes with therapeutic alternatives. This category allows payors to equalize the margins and payments to providers between high-cost branded therapies and the LCA. This is accomplished by calculating the brand drug margin per claim based on the physician's actual acquisition cost and applying that equivalent dollar margin to the LCA's acquisition cost. Clinical objectives are addressed in program design and development while prescribers are compensated with a fair and typical margin for prescribing preferred therapies. Likewise, for high-cost MAC drugs, a fair and typical margin is provided for high-dollar claims, versus a set percentage markup. Finally, a fourth reimbursement category based on average wholesale priced base reimbursement would remain available for drug codes where ASP-based pricing is unavailable.

Medical Formulary Opportunities

The preceding discussions focus on the potential benefits of implementing medical formularies. For example, the application of well designed, comprehensive medical formulary management programs can impact the bottom line in meaningful ways. Several medical drug categories, including those listed above, present opportunities to generate savings through appropriate management.

- Oncology supportive care
- Inflammatory categories (e.g., RA, GI, dermatology)
- Viscosupplementation
- Botulinum toxins
- Long-acting reversible contraceptives
- Gaucher's disease

Management opportunities may include the implementation of a variable reimbursement fee schedule, with a maximum allowable cost/least cost alternative product selection strategy. Additionally, targeted strategies may be applied to promote generic utilization and equalize margins on products within several therapeutic classes, including intravenous immunoglobulin (IVIG), taxanes, folinic acids, ophthalmic injections, viscosupplementation, and antiemetics. The potential impact of implementing these programs can be significant. For example, in the antiemetic category, removing incentives for physicians to prescribe higher-cost, branded antiemetics, rather than the low-cost preferred alternatives, has the ability to generate meaningful savings.

Conclusion

Opportunities for improving outcomes and managing costs through the management of medical drug spending are both abundant and challenging. Payors are tasked with coordinating the sometimes divergent priorities and influences in health care. Clinical and economic objectives may at times conflict; claims adjudication and electronic medical record systems may not sufficiently support data capture, analysis, and reporting needs; misalignment of payor and provider priorities creates challenges, particularly with regard to reimbursements, distribution channel, and site of care management. However, a systematic, patient-centered and data-driven approach to assessing costs, identifying opportunities, developing interventions, and coordinating care across the health care setting will assist stakeholders in attaining clinical and economic objectives through the effective use of medical pharmacy management strategies.

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MAGELLAN TREND REPORT:

Key Insights Into Developing Strategies for Medical Benefit Specialty Drug Management

Casey Stockman, PharmD, Vice President, Medical Pharmacy Strategy, Magellan Rx Management

Casey Stockman
PharmD

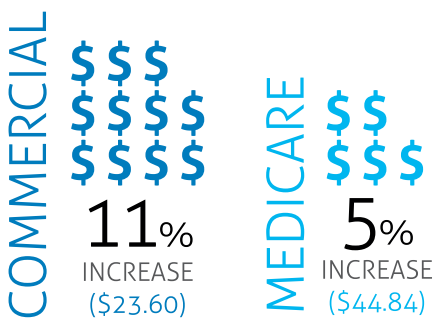
Insight regarding medical benefit drug spending has been notoriously limited, despite the fact that an estimated 50 percent of $124 billion[1] in annual specialty drug spend is billed to the medical benefit, and specialty drug costs remain the leading driver of overall drug trends. Now in its sixth edition, the Magellan Rx Management *Medical Pharmacy Trend Report*™ offers valuable insights on medical pharmacy spending, serving as the only detailed source for current approaches to medical benefit drug management and data benchmarking.

The *Trend Report*™ is derived from two sources: a survey of key stakeholders from 59 commercial payors, representing approximately 130 million covered lives, considered alongside an in-depth analysis of commercial and Medicare Advantage health plan medical paid claims data. Collectively, the *Trend Report*™ provides insight into medical pharmacy utilization across all outpatient sites of service, including physician offices, home infusion providers, specialty pharmacies, and hospital outpatient facilities.

Among other findings, the 2015 *Trend Report*™ offers key insights into the impact of inflation, utilization, drug mix, and shifts in site of service on medical pharmacy spending. In 2014, per-member-per-month (PMPM) allowed amounts rose by 11 and 5 percent for Commercial and Medicare Advantage plans, respectively, with commercial PMPM growing to $23.60 while Medicare PMPM rose to $44.84. Data indicate commercial patients were twice as costly to manage as Medicare subscribers ($22,423 vs. $10,551) when considering the average annual cost per patient for the top 25 drugs by spend. This is demonstrated in Tables 1 and 2.

Oncology and oncology-support medications represent the largest share of 2014 medical benefit drug spend, accounting for 52.8 percent of medical pharmacy costs for commercial plans and, even more significantly, 63.1 percent of Medicare costs. The second leading drivers of cost differed between these segments. Biologic drugs for autoimmune disorders (BDAIDs) accounted for 15.3 percent of commercial spending. These consist of treatments for Crohn's disease/

Table 1: Trends* in PMPM Allowed Amounts[1]



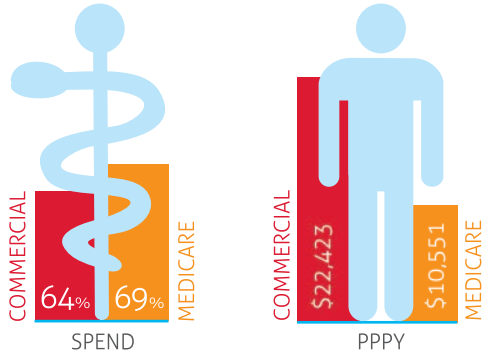
*The most recent year of medical benefit paid claims data analyzed in our 2015 trend report is from 2014 due to the lag associated with medical benefit claims processing and time needed for publishing.

ulcerative colitis, rheumatoid arthritis, and other inflammatory conditions. Meanwhile, the second most significant driver of costs for the Medicare population, accounting for 9 percent of spending, was ophthalmic injections or anti-vascular endothelial growth factor intravitreal injections for treatment of retina diseases.

Additionally, the *Trend Report*™ explores utilization patterns that influence spending, such as the impact of shift of site of service on costs. For example, movement of provider-administered drugs from the physician office to hospital outpatient facilities remains a key driver of medical pharmacy spending. For commercial payors, costs billed from hospital outpatient facilities increased to 53 percent in 2014, up from 47 percent in 2010. For the same time period, the shift in the Medicare segment rose to 40 percent of costs billed from hospital outpatient facilities, up from 24 percent in 2010. The *Trend Report*™ cites data indicating that administrative code reimbursement is four times more expensive in the hospital outpatient setting than the physician office for commercial members. For Medicare, hospital outpatient setting administration code costs are twice those of the physician office.

Benefit design factors that influence pharmacy costs, such as product preferencing, are also explored within the *Trend Report*™. Ninety-two percent of payors report having product preferencing in place, with the top therapeutic classes for this strategy being identified as BDAIDs, viscosupplementation, and multiple sclerosis. Payor insights regarding the use of strategies such as step edits to support attainment of rebates, or varying member cost share by drug or site of service, are investigated as well. Approximately 13 percent of payors varied cost share requirements for members by drug, and 23 percent reported varying cost share by site of service during 2015. Among payors indicating they did not currently vary member cost share by drug or site of service, 35 percent indicated they had the capability to vary member cost share by drug in the future, while 49 percent could modify patient cost share by site of service.

Table 2: Top 25 Drugs[1]



Finally, the *Trend Report*™ provides unique insights into the pharmacy provider network landscape and national provider trends, explores the future outlook of the medical benefit drug pipeline, and investigates legislative reimbursement policy updates that affect medical pharmacy management and providers. The Magellan Rx Management *Medical Pharmacy Trend Report*™, a valuable resource offering a perspective of the key drivers of medical pharmacy costs and potential strategies for their management, is available for download at **magellanrx.com**.

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Long-Acting Injectable Antipsychotics: A Solution to Nonadherence?

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In 2014, about 9.8 million American adults (4.1 percent of all adults) were living with serious mental disorders.*[1] Among the most troublesome disorders contributing to these numbers are schizophrenia, schizoaffective disorder, and bipolar disorder, which impair multiple facets of functioning. They impose a substantial disease burden on patients, patients' relatives and friends, the health care system, and society. These illnesses tend to emerge in late adolescence or early adulthood, thereby greatly diminishing the ability of many patients to participate fully, if at all, in vocational and social activities (see Table 3). They also reduce life expectancy by about 10 to 20 years.[2] In the nonelderly Medicaid population, patients with schizophrenia lost a mean of 28.5 years per death.[3] Compared with the general population, patients with bipolar disorder and schizophrenia are at approximately a 15 times higher risk of suicide.[2] Long-acting injectable antipsychotics (LAIs) present opportunities to improve outcomes for patients with schizophrenia, schizoaffective disorder, and bipolar disorder. Due to the nature of these disorders, many patients may find it difficult to adhere to daily oral treatment intended to improve their quality of life and prevent relapse, notably psychotic episodes. However, LAIs also could improve quality of life even for patients who do adhere to a daily regimen.

The year 2016 marks the 50th anniversary of the development of the first LAI, fluphenazine enanthate (Prolixin®).[4] Initially viewed skeptically by physicians, LAIs were gradually accepted by the medical community as evidence emerged supporting their use to improve outcomes by enhancing patients' adherence to therapy. Their popularity later waned, however, as the drugs acquired a stigma, being characterized as "chemical straitjackets" by some opponents.

LAIs came into use in a social context where patients with schizophrenia were moving from institutions into communities, with relatives assuming much of the responsibility for helping patients adhere to therapy. Continuing emphasis on deinstitutionalization of patients with mental illness and increased reliance on outpatient and community health care intensified interest in LAIs. By 1990, LAIs were administered to about 80 percent of outpatients with psychosis in the United Kingdom, but to only 12 to 20 percent in the United States.[4]

Low utilization of LAIs in the United States may have occurred because they came to be regarded as tools of last resort, reserved for treating patients perceived as problematic.[5] Glazer argued that if LAIs were prescribed to address the rate of nonadherence — estimated at > 50 percent — in the U.S. schizophrenia population, the point prevalence of LAI use in this population would be about only 10 to 15 percent.

Schizophrenia, schizoaffective disorder, and bipolar disorder share some common characteristics (see Figure 1) that may complicate and delay diagnosis and therapy. All three require a multidisciplinary, lifelong approach, of which drug therapy is a mainstay. The general pharmacologic approach to the disorders consists of treatment of acute exacerbations and maintenance therapy to reduce the risk of relapse and hospitalization. Many patients who adhere to drug therapy can lead relatively normal lives. Yet the nature of the disorders is such that nonadherence to a drug regimen becomes problematic.

**Defined in the National Survey on Drug Use and Health as a mental, behavioral or emotional disorder (excluding developmental and substance use disorders) diagnosed currently or within the past year, of sufficient duration to meet diagnostic criteria in DSM-4 and resulting in serious functional impairment that substantially limits ≥ 1 major life activity. Thus, by this definition, a given diagnosis (e.g., bipolar disorder) is insufficient in itself to qualify as a serious mental illness in the absence of serious functional impairment.*

The three disorders share a tangled history in the medical literature, with controversy over their classification continuing to this day. Around the end of the 19th century, the eminent German psychiatrist Emil Kraepelin (1856–1926) was the first to differentiate schizophrenia (then called dementia praecox, until the influential Swiss psychiatrist Eugen Bleuler introduced schizophrenia in 1911) from bipolar disorder (then called manic-depressive insanity), but by 1920, Kraepelin had found it difficult to distinguish one from the other.[6] In 1933, Jacob Kasanin introduced schizoaffective disorder as an intermediary diagnosis to accommodate patients for whom a diagnosis of schizophrenia or bipolar disorder seemed inadequate, and he regarded schizoaffective disorder as having a better outcome, a view that has become outmoded. In fact, compared with patients with schizophrenia, patients with schizoaffective disorder are at greater risk of hospitalization, suicide, and substance abuse, and they may account for one-fourth of acute psychiatric admissions.[7] Nearly every edition of the *Diagnostic and Statistical Manual* (DSM) has treated schizophrenic disorder differently, in terms of terminology and diagnostic criteria (see Table 1).

Diagnostic Uncertainty

A study demonstrating the substantial uncertainty surrounding these diagnoses employed a population of 134 psychiatrically hospitalized patients in Tennessee, including 48 with a clinical diagnosis of schizophrenia, 50 with schizoaffective disorder, and 36 with bipolar disorder with psychotic features.[10] When trained researchers applied the Structured Clinical Interview from DSM-4-TR to the population, they agreed that 42 patients had schizophrenia — but the researchers also diagnosed schizophrenia in 17 patients initially diagnosed clinically with schizoaffective disorder, along with five whose clinical diagnosis was bipolar disorder. Compared with the clinicians, the researchers diagnosed fewer patients with schizoaffective disorder, agreeing that 30 patients had schizoaffective disorder but also classifying five clinical diagnoses of schizophrenia and one clinical diagnosis of bipolar disorder as schizoaffective disorder. The researchers agreed with the clinical diagnosis of bipolar disorder in 28 patients, but they determined that five patients with a clinical diagnosis of schizophrenia and three with a clinical diagnosis of schizoaffective disorder had bipolar disorder instead. Figure

Table 1: Schizoaffective Disorder Through the Years in the *Diagnostic and Statistical Manual* (DSM)[8,9,47]

Edition (year)	Year	
DSM, first edition	1952	Terminology used: schizophrenic reaction* and schizoaffective type
DSM-2	1968	Schizoffective type divided into excited and depressed subtypes
DSM-3	1980	First use of schizoaffective disorder, but without diagnostic criteria
DSM-3-Text Revision (TR)	1987	Diagnostic criteria added, with a bipolar type (current or previous manic syndrome) and a depressed type (no current or previous manic syndrome)
DSM-4	1997	Mixed episodes added to bipolar type
DSM-4-TR	2000	No change
DSM-5	2013	Instead of exhibiting just a single symptom, patient is required to exhibit ≥2 specified symptoms: • Delusions • Hallucinations • Disorganized speech • Grossly organized or catatonic behavior • Negative symptoms Subtypes eliminated (bipolar type, depressed type) because they weren't useful for clinicians

**The diagnosis* schizophrenia *does not appear in DSM-1.* Schizophrenic reaction *is used instead*

2 shows the distribution of clinical and research diagnoses in this population.

Researchers have employed different approaches to determine how the three diagnoses compare and contrast with one another. In a systematic review of neurocognitive and neuroimaging studies using well-defined populations of patients with schizoaffective disorder, cognitive performance tended to be worse in patients with schizophrenia and schizoaffective disorder than in patients with bipolar disorder.[6] An international study using sociodemographic and clinical measures for 2,269 patients with psychosis found that schizoaffective disorder ranked between schizophrenia and bipolar I disorder, with schizoaffective disorder tending to be more severe than bipolar I disorder but less severe than schizophrenia.[11]

Whatever the methodology, researchers have tended to assign schizoaffective disorder to an intermediate position between schizophrenia and bipolar disorders or sometimes as a subcategory of schizophrenia. Shifting definitions have complicated epidemiological and clinical research over the years to the point that uncertainty about the diagnosis lies behind the paucity of studies on schizoaffective disorder relative to schizophrenia and bipolar disorder.[12]

Prevalence and Disease Burden

Schizophrenia and schizoaffective disorder. The median lifetime morbid risk of schizophrenia is 7.2 per 1,000, meaning that about seven people in 1,000 already have developed or can be expected to develop schizophrenia in their lifetimes.[13]

Median lifetime prevalence of schizophrenia (the proportion of people living with the disorder) is 4.0 per 1,000.[13] The prevalence of schizoaffective disorder is generally thought to be one-third that of schizophrenia, which is born out by a Finnish study in which lifetime prevalence of schizoaffective disorder and schizophrenia was estimated at 0.32 and 0.87 percent, respectively.[14]

Due to the absence of more current statistics, using medical claims data, researchers estimated the 12-month prevalence of *diagnosed* schizophrenia in the United States to be about 0.5 percent, or 1.5 million people.[15] They also estimated 12-month prevalence by type of insurance coverage in 2002, finding its prevalence highest in the Medicaid population, 1.66 percent; followed by uninsured, 1.02 percent; Medicare, 0.83 percent; and private insurance, 0.13 percent.

The most recent estimate of the economic burden of schizophrenia in the United States placed overall costs at $63 billion in 2002.[16] Direct health care costs accounted for $23 billion, of which 35 percent went to long-term care, 31 percent to outpatient care, 22 percent to drug treatments and 12 percent to inpatient care. Reducing the risk of relapse and hospitalization in patients with psychotic disorders is critical for constraining health care spending, as shown by the disparity in costs between patients who do or do not experience illness-related crises.

Direct nonhealth care costs for schizophrenia in 2002 were estimated at $9 billion, with homeless shelters accounting for two-thirds of this amount, because about 21 percent of the U.S. homeless population was estimated to have schizophrenia.[16]

Table 2: Differences Between Bipolar I and Bipolar II Disorders[17,18,48]		
	Bipolar I	Bipolar II
Lifetime prevalence, U.S.	1.0%	1.1%
12-month prevalence, U.S.	0.6%	0.8%
Presence of major depressive episodes	Yes	Yes
Presence of manic episodes	Yes — a distinct period of abnormally and persistently elevated, expansive, or irritable mood that lasts ≥ 1 week	Never — patients have hypomania, a sustained mood that is noticeably different from normal nondepressed mood, but not extremely so; persists ≤ 4 days. Any manic episode would result in different diagnosis.
Presence of psychotic symptoms during manic or hypomanic episodes	Yes	Never (but patients may experience psychotic symptoms during depressive episodes)
Hospitalization required for manic or hypomanic episodes	Often	Rarely
Effect of mania/hypomania on daily functioning	Mania substantially interferes with daily functioning	Hypomania interferes with daily functioning to some extent

Bipolar disorders. The two major types of bipolar disorder are bipolar I, characterized by major depressive episodes and mania, and bipolar II, characterized by major depressive episodes and hypomania (and never a manic episode). In bipolar I disorder, the mania can greatly impair social and occupational functioning and include psychotic symptoms, and it often leads to hospitalization. In contrast, the hypomania of bipolar II does not impair functioning to any great extent and rarely requires hospitalization, but the longer periods of major depression in bipolar II can cause substantial impairment (see Table 2).

Bipolar disorders are considerably more common than schizophrenia or schizoaffective disorders, though estimates differ. By one estimate, the lifetime prevalence of bipolar I and II disorders in the United States is 3.9 percent.[19] By age group, prevalence is highest among adults ages 18 to 29 (5.9 percent), followed by those 30 to 44 years of age (4.5 percent). The 12-month prevalence of bipolar I and II disorders is 2.6 percent, with 82.9 percent of cases considered serious.[20] In a U.S. probability sample, lifetime prevalence of bipolar I and bipolar II disorder was estimated at 1.0 and 1.1 percent, respectively, and 12-month prevalence of bipolar I and bipolar II disorder was estimated at 0.6 and 0.8 percent, respectively.[18] This study also estimated the prevalence of subthreshold bipolar disorder and found it to be common, with lifetime and 12-month prevalence rates of 2.4 and 1.4 percent, respectively.

As of 2009, the total cost of bipolar I and II disorders in the United States was estimated at $151 billion, including $31 billion in direct costs and $120 billion in indirect costs but excluding costs of subthreshold bipolar disorder.[21]

Second-Generation LAIs

Oral antipsychotics are the mainstay of drug therapy for treating acute symptoms and as maintenance treatment to prevent relapse in patients with psychotic disorders. LAIs offer an intuitively attractive option for patients who have difficulty adhering to an oral regimen.

First- and second-generation antipsychotics (FGAs and SGAs, also known as typical and atypical antipsychotics, respectively) differ primarily in their adverse-effect profiles. FGAs are associated with extrapyramidal symptoms (movement disorders), along with dry mouth and sedation, and more rarely, neuroleptic malignant syndrome and tardive dyskinesia. These adverse events are seen less often in SGAs, which instead tend to be associated with metabolic adverse effects, such as weight gain, elevated lipid levels, and type 2 diabetes.[22] When SGAs were developed, it was assumed that they would be more efficacious than FGAs, but this hope has not been borne out by comparative effectiveness research.[23] Because SGAs tend to have only modestly better efficacy, if any, than FGAs, adverse-effect profiles have been an important

Oral antipsychotics are the mainstay of drug therapy for treating acute symptoms and as maintenance treatment to prevent relapse in patients with psychotic disorders. LAIs offer an intuitively attractive option for patients who have difficulty adhering to an oral regimen.

factor behind drug selection and patient adherence to therapy. Adverse-effect profiles can differ considerably among SGAs, however.

Six second-generation atypical antipsychotics are marketed in the United States as LAIs (see Table 4): aripiprazole lauroxil (Aristada®, Alkermes), aripiprazole monohydrate (Abilify Maintena®, Otsuka), olanzapine pamoate (Zyprexa® Relprevv™, Eli Lilly), once-monthly paliperidone palmitate (Invega Sustenna®, Janssen), paliperidone palmitate every three months (Invega Trinza®, Janssen), and risperidone (Risperdal Consta®, Janssen). Each of the six is indicated for treatment of schizophrenia. Paliperidone once-monthly also is indicated as a maintenance therapy for schizoaffective disorder, as either monotherapy or adjunct. Risperidone also has a second indication, as maintenance treatment for bipolar I disorder, either as monotherapy or adjunct. Among these six LAIs, dosing intervals range from every two weeks (risperidone) to every three months (paliperidone [Invega Trinza]).

SGA LAIs vs. oral SGAs or FGA LAIs. Clinicians and patients, however, tend to be more interested in how SGA LAIs compare with oral antipsychotics or FGA LAIs. These are questions for which definitive answers have not yet been obtained.[23,24] Several large recent trials have addressed these topics, even as they raise more questions: LAIs present numerous advantages and disadvantages (see Table 5), but uncertainty about when and how LAIs should be used remains.

Risperidone LAI vs. oral antipsychotics. In the 30-month PROACTIVE (Preventing Relapse Oral Antipsychotics Compared to Injectables Evaluating Efficacy) study at eight academic centers, community-dwelling patients with schizophrenia or schizoaffective disorder (n = 305) were randomly assigned to risperidone LAI or oral SGA (physician's choice, to reflect real-world conditions) to evaluate time to first relapse and hospitalization.[25] The study was supported by the National Institute of Mental Health (NIMH), and risperidone LAI was selected because it was the only SGA LAI on the U.S. market when PROACTIVE began in 2006. Patients in the oral SGA group received six different SGAs, as follows:

- olanzapine (20 percent)
- aripiprazole (14 percent)
- ziprasidone (9 percent)
- paliperidone (6 percent)
- quetiapine (5 percent)
- iloperidone (1 percent)

The oral SGA was changed for 28 percent of subjects during study treatment. Treatment was discontinued by 53 percent of subjects before study end, including 81 in the risperidone LAI group and 80 in the oral SGA group. Relapse rates were 42 percent (61/146) and 32 percent (48/150) in the risperidone LAI and oral SGA groups, respectively, but the difference was not statistically significant. Differences in time to first relapse or first hospitalization also were not statistically significant.

Similar results were seen in an earlier study, with a similar design, of risperidone LAI versus psychiatrist-selected oral antipsychotics.[26] The study enrolled 369 patients

Figure 1: Shared Clinical Features of Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder[36]

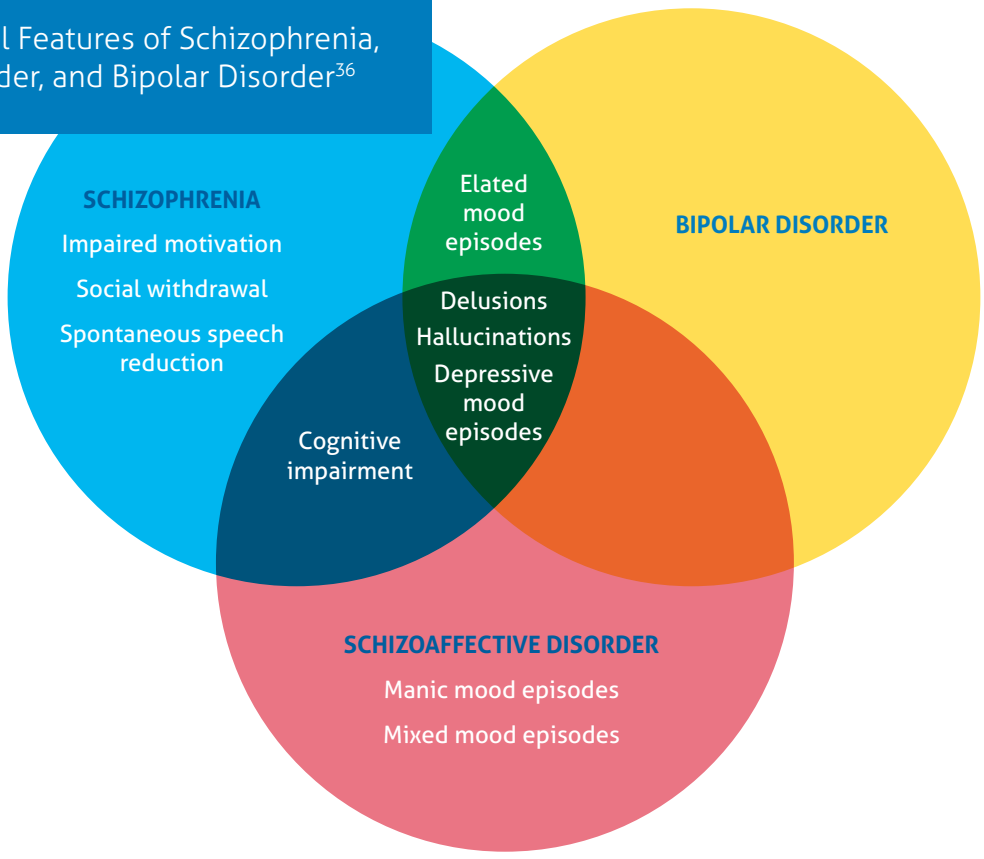


Table 3: Schizophrenia Signs and Symptoms[36,38]

Symptoms	Comments
Positive (psychotic symptoms)	1st psychotic episode usually in late adolescence/early adulthood
• Delusions	• Onset may be sudden, but
• Hallucinations	• Impaired cognition and/or impaired social functioning may precede 1st episode by several years
• Thought disorder	Long-term persistence possible
• Bizarre behavior	May stem from abnormal glutamate signaling
	Tend to relapse and remit
	May stem from abnormal dopamine transmission
	Long-term maintenance therapy often prevents relapse, at the expense of various side effects, but in many patients, existing antipsychotics are only partially effective, if at all
Negative	Usually chronic, affecting social functioning
• Impaired motivation	Severity can vary from patient to patient
• Social withdrawal	
• Reduced speaking	
• Flat affect	
Cognitive deficits	Usually chronic, affecting social functioning
• Executive functioning	Along with functional decline, these deficits often precede onset of psychosis
• Attention/vigilance	May affect severity of social and occupational dysfunction later in illness
• Working memory	
• Reasoning/problem-solving	
• Verbal comprehension	
• Social cognition	

with unstable schizophrenia or schizoaffective disorder in the Veterans Affairs system. At randomization, 40 percent were hospitalized, 55 percent had been hospitalized within the past two years, and 5 percent were deemed at risk of hospitalization. After randomization, the rates of hospitalization were 39 percent (72/187) after 10.8 months of follow-up and 45 percent (81/182) after 11.3 months of follow-up in the risperidone LAI and oral antipsychotic groups, respectively; the difference was not statistically significant.

Newer vs. older LAIs. In another NIMH-funded study, patients with schizophrenia or schizoaffective disorder known to have a history of medication nonadherence or substance abuse, or both, were enrolled to compare the SGA LAI paliperidone with an older FGA LAI, haloperidol.[27] The investigators hypothesized that paliperidone LAI would be associated with lower rates of efficacy failure (defined by psychiatric hospitalization and other criteria), but no statistically significant difference in rate of this measure was found (32.4 percent [47/145] in the haloperidol group versus 33.8 percent [49/145] in the paliperidone group).

The NIMH also funded a study to determine whether patients with schizophrenia or schizoaffective disorder who were taking the first-generation LAI haloperidol decanoate (n = 40) or fluphenazine decanoate (n = 22) would benefit from switching to second-generation risperidone LAI.[28] The study enrolled patients suboptimally controlled but not requiring an immediate switch. The authors noted that such a switch would have substantial cost implications, given the dramatically higher price of risperidone LAI versus the older LAIs. Patients were randomly assigned to switch to risperidone LAI (n = 24) or stay with their first-generation LAIs (n = 29), and they were required to continue the assigned treatment for six months (unless it was clinically contraindicated), followed by six months of naturalistic follow-up. Treatment was open-label but assessment by clinicians was blinded. During the initial six-month period, there was no clinically significant difference in time to all-cause treatment discontinuation, the prime outcome. When the additional six-month period of naturalistic follow-up was added to the initial six-month period, the rate of discontinuation was higher in the group switched to risperidone than in the group that remained on their first-generation LAIs

(31 percent versus 10 percent). Over time, expected changes in body mass index (BMI) did occur — an increase in BMI among patients who were switched to risperidone LAI versus a decrease in BMI among patients who stayed with their first-generation LAIs. Expected changes in prolactin also favored the first-generation LAI over risperidone LAIs.

LAIs vs. oral SGAs. In a retrospective industry-supported study, two matched cohorts (n = 335 in each) of patients with schizophrenia were drawn from the Veterans Health Administration (VHA) database. Patients treated with monthly paliperidone had lower health care utilization and costs than patients treated with oral atypical antipsychotics over a 12-month period.[29] The mean number of hospitalizations in the paliperidone cohort and the oral cohort was 0.8 versus 1.3, respectively, while the mean number of inpatient days per patient was 13.2 versus 24.2, respectively. Although mean pharmacy costs were higher in the paliperidone cohort ($10,063 versus $4,167), inpatient costs were lower in the paliperidone cohort ($18,560 versus $31,505), as were total costs ($45,529 versus $53,569), although the difference in total costs was not statistically significant.

Differences between the cohorts suggest that once-monthly paliperidone had been used in more difficult patients during the 24-month interval preceding the 12-month period for which health care utilization and costs were determined: Nearly twice as many patients in the paliperidone cohort had received multiple antipsychotics (82 percent versus 43 percent) during the baseline period, and the percentage of patients with three or more hospitalizations also was higher in the paliperidone cohort (28 percent versus 20 percent).

Black-box warnings. Like the package inserts for oral antipsychotics, the package inserts for all six second-generation LAIs contain a black-box warning stating that they are not approved for treatment of patients with dementia-related psychosis and that elderly patients with dementia-related psychosis are at increased risk of death if treated with antipsychotic drugs.

The olanzapine LAI prescribing information contains an additional black-box warning about post-injection delirium/sedation syndrome. After an injection of olanzapine LAI, patients are at risk of severe sedation (including coma) or delirium, or both. In premarketing clinical trials, events characterizing the syndrome occurred in < 0.1 percent of injections, but in 2 percent of patients who received injections for up to 48 months; the risk is cumulative, increasing with the number of injections received. Most patients were hospitalized, some requiring supportive care, but all were largely recovered by 72 hours. Because of the risk of this syndrome, the drug is available only through a restricted distribution program in which the prescriber, health care facility, and pharmacy must enroll. After each injection, the patient must be continually observed by a health care professional for three hours or more in a registered facility with ready access to emergency response services. Upon discharge, patients must be accompanied to their destinations.[30]

Opportunities for Health Plans to Improve Care

Opportunities abound for health plans to improve the care of patients with psychotic disorders and for making that care more efficient.

Early detection and intervention. Duration of untreated psychosis (DUP) is the interval between the first episode of psychosis and the initiation of drug therapy to treat it. Long DUP is associated with high levels of positive symptoms and impaired social functioning up to two years later.[31] The recommended standard for initiating therapy for a first psychotic episode is less than three months.[32]

In the United States, programs to improve DUP have not been widely adopted by health plans or other organizations, which may explain the far longer DUP experienced by patients seen at community mental health centers. In a nationwide study sponsored by the NIMH involving 34 nonacademic mental health clinics in 21 states, median DUP was 74 weeks for the 404 participants presenting with first-episode psychosis.[33] For schizophrenia (n = 214) and schizoaffective disorder (n = 81), median DUP was 99 and 138 weeks, respectively.

Health plans also should encourage primary care providers to screen for bipolar disorders whenever a patient presents with depressive symptoms to shorten the time between disease onset and diagnosis.

Improving adherence in general. Poor adherence to drug therapy is common among patients with psychiatric disorders. A review of the literature in which compliance was quantified found that patients receiving antipsychotics took, on average, 58 percent of the recommended amount of their drugs (range, 24–90 percent), whereas patients receiving antidepressants took 65 percent (range, 40–90 percent).[34] In comparison, nonpsychiatric patients receiving drugs for physical disorders took about 76 percent of doses as prescribed.

An implication of this study that is important for health plans is that the substantial percentage of patients who receive antipsychotic drugs concurrently with drugs for comorbid physical disorders are likely to be just as nonadherent to their nonpsychiatric drugs if they are nonadherent to their antipsychotics. Even if LAIs satisfactorily address a problem with antipsychotic nonadherence, patients may continue to be nonadherent to their other drug regimens, resulting in poor outcomes and increased health care spending.

In the interest of improving outcomes and reducing health care costs, it is insufficient to treat psychiatric disorders, using LAIs or not, without also attending to the numerous comorbid conditions associated with them. Thus, management of schizophrenia extends to a focus on cardiovascular health, as even young adults with schizophrenia experience excess cardiovascular mortality.[3] Health plans should remind providers that patients taking any antipsychotic, whether LAI or oral, should be monitored regularly for metabolic and neurologic adverse effects.[35] The presence of these adverse effects demonstrates a continuing need for new antipsychotics with fewer adverse effects, especially metabolic adverse effects that lead to cardiovascular events.[36]

Table 4: LAI Antipsychotic Indications and Pricing[30,42-46]

Drug	Manufacturer	Indication	WAC‡	ASP‡‡+ 6%
Abilify Maintena® 300mg (aripiprazole)	Otsuka	Schizophrenia	$1,282.84	$1,318.80
Abilify Maintena 400mg (aripiprazole)			$1,710.45	$1,758.40
Aristada™ (aripiprazole lauroxil) 441mg/1.6mL	Alkermes	Schizophrenia	$1,055.00	$1,335.35
Aristada (aripiprazole lauroxil) 662mg/2.4mL			$1,583.00	$2,004.54
Aristada (aripiprazole lauroxil) 882mg/3.2mL			$2,109.00	$2,670.70
Zyprexa Relprevv™ (olanzapine) 210mg	Eli Lilly	Schizophrenia	$589.68	$612.57
Zyprexa Relprevv (olanzapine) 300mg			$842.40	$875.10
Zyprexa Relprevv (olanzapine) 405mg			$1,137.24	$1,181.39
Invega Sustenna® (paliperidone palmitate) 39mg/0.25mL	Janssen	Schizophrenia and Schizoaffective Disorder	$351.30	$353.22
Invega Sustenna (paliperidone palmitate) 78mg/0.25mL			$702.65	$706.45
Invega Sustenna (paliperidone palmitate) 117mg/0.75mL			$1,053.97	$1,059.67
Invega Sustenna (paliperidone palmitate) 156mg/1mL			$1,405.36	$1,412.89
Invega Sustenna (paliperidone palmitate) 234mg/1.5mL			$2,107.99	$2,119.34
Invega Trinza® (paliperidone palmitate) 273mg/0.875mL	Janssen	Schizophrenia after patients have been adequately treated with Invega Sustenna for at least 4 months	$2,107.99	$2,472.56
Invega Trinza (paliperidone palmitate) 410mg/1.315mL			$3,161.93	$3,713.97
Invega Trinza (paliperidone palmitate) 546mg/1.75mL			$4,216.06	$4,945.12
Invega Trinza (paliperidone palmitate) 819mg/2.625mL			$6,323.96	$7,417.68
Risperdal Consta® (risperidone) 12.5mg	Janssen	Schizophrenia, Bipolar I Disorder	$191.81	$194.03
Risperdal Consta (risperidone) 25mg			$383.57	$388.05
Risperdal Consta (risperidone) 37.5mg			$575.39	$582.08
Risperdal Consta (risperidone) 50mg			$767.20	$776.10

‡ *Wholesale Acquisition Cost (based on Micromedex, Red Book)* ‡‡ *Average Sales Price (based on CMS ASP Pricing File)*

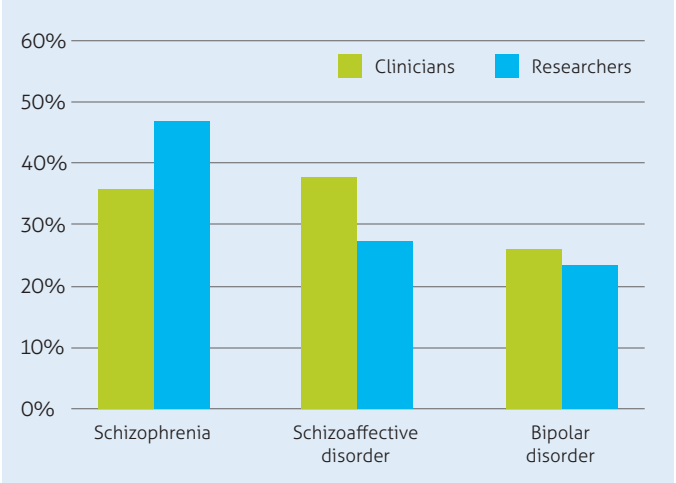
More attention — screening, counseling, evidence-based treatment — also must be given to smoking, which is highly prevalent among people with schizophrenia, and contributes to premature mortality in this population from lung cancer, COPD, and pneumonia and influenza, along with cardiovascular disease.[3]

Use of LAIs. Patients for whom LAIs might be appropriate extend beyond those with a history of nonadherence or who are thought to be at high risk of nonadherence. Some patients simply may desire the convenience afforded by once-monthly or even once-quarterly injections. Other patients or their relatives or caregivers may feel overwhelmed by polypharmacy, in which case an LAI could simplify a complicated multidrug regimen and improve overall adherence. When an antipsychotic is under consideration, health plans should encourage providers to make patients aware that LAI formulations are available. In its practice guideline for schizophrenia, the American Psychiatric Association recommends LAIs be considered for patients with recurrent relapses related to nonadherence or for patients who prefer LAIs.[37]

Prescribers should look beyond the atypical class when selecting an LAI, because a first-generation drug may be appropriate for some patients, and that drug is likely to be priced much lower than a second-generation LAI.

Because of the waxing and waning nature of psychotic disorders, LAIs should be considered for patients experiencing their first psychotic episode because such patients may discontinue oral therapy when they feel better, thinking it no longer is needed.[35] Early treatment with an LAI can reduce the risk of relapse. If LAI therapy is initiated during hospitalization, care needs to be coordinated with outpatient clinicians so that the LAI is continued, and the initial drug should be one with adequate health insurance coverage.[35]

Figure 2: Distribution of Clinical and Research Diagnoses in the Same Hospitalized Population[10]



Distribution of diagnoses as made by clinicians and trained researchers in the same population of 134 patients at Vanderbilt Psychiatric Hospital. The initial clinical diagnoses were schizophrenia (n = 48), schizoaffective disorder (n = 50), and bipolar disorder (n = 36). Substantial disagreement about diagnoses became evident when researchers applied the Structured Clinical Interview from DSM-4-TR to this population.

Because patients with schizophrenia are at risk of rehospitalization during the post-discharge period, more interactions with recently discharged patients (counseling, post-discharge plans) may be useful to reduce health care spending.[12]

If a patient is unable or refuses to take an oral medication, an LAI that does not require concurrent administration with an oral antipsychotic is recommended, such as haloperidol LAI or paliperidone LAI.[35]

Using LAIs seems intuitive and attractive as a solution to the vexing problem of nonadherence to oral antipsychotics. Head-to-head studies that fail to show a meaningful difference between LAIs and oral antipsychotics may reflect the inadequacy of clinical trials for investigations in which real-world adherence or nonadherence is of central concern. By their nature, formal clinical studies explicitly or implicitly promote improved adherence, making "real-world" studies more useful for learning about the effects of LAIs on adherence.

Prescribing an LAI cannot completely eliminate the problem of nonadherence, simply because patients can become nonadherent to LAIs by failing to appear for their scheduled injections. In that event, however, health care providers do have perfect knowledge of a patient's treatment status, and if a patient fails to keep an appointment, they should have a plan ready to implement immediately to help the patient resume treatment. Such a plan should be discussed with the patient and the patient's relatives and caregivers at the time of LAI initiation so that all parties have full knowledge of proposed actions and responsibilities.

Opportunities for Scholars and Researchers

High-risk patients. The disease burden imposed by psychotic disorders may be lightened by identifying people at high risk of developing them. During the prodrome, an interval (weeks to years) prior to the onset of psychosis, many people display psychological and behavioral abnormalities. The prodrome typically has been identified retrospectively, but research has been aimed at identifying it prospectively.[38] The clinical challenge is that while about 20 to 30 percent of people prospectively identified (through structured interviews) as being in a prodromal period eventually convert to schizophrenia or another psychotic disorder over the course of two or three years, a high rate of false positives could result in stigmatization or unnecessary treatment, or both.[39]

Biomarkers. A more fruitful approach to identifying people at high risk of developing a psychotic disorder may be the development of a panel of protein-based serum biomarkers with high diagnostic accuracy in identifying prodromal patients as well as apparently psychologically healthy people at high risk of converting to schizophrenia.[39] This panel is envisioned as being used in conjunction with structured interviews, not as a tool to screen the general population.

Progress toward the development of a similar blood-based biomarker panel to diagnose bipolar disorder also has been

Table 5: Advantages and Disadvantages of LAIs and Barriers to Their Use[23,35,47]

Advantages	Disadvantages	Barriers
Reduced concern about adherence to drug therapy — health care provider has perfect knowledge of whether or not drug has been administered	Does not solve problem of nonadherence if patient chooses to discontinue LAI	Delay in making diagnosis
Simplified decision making by patients on taking medication — 1 or 2 decisions per month for LAIs vs. 1 or 2 decisions per day for oral antipsychotics	Price of SGA LAI may be considerably higher than oral antipsychotic or FGA LAI	Misdiagnosis
Simplified drug regimen for patients	Requires travel to a clinic or home visitation	Physicians' underestimation of rate of nonadherence in their patients
Elimination of nonadherence as explanation for any relapse that occurs	Requires injection, with injection-site pain or skin irritation or lesions possible	Physicians' failure to present LAI to their patients as on option
Impossibility of patients overdosing on injected antipsychotic; reduced risk of overdose by any means	At LAI initiation, period of overlap with the oral formulation may be necessary to attain therapeutic levels	Restricted formularies
		Patients' perception of LAI as threat to their autonomy or as stigma
		Fear of injections
		Unwillingness or inability of patients to go to clinic for injection

reported.[40] It too would be used in conjunction with clinical interviews to diagnosis bipolar disorder before the onset of manic or hypomanic symptoms. Currently, it often takes many years before bipolar disorder is correctly diagnosed because patients often present with depressive symptoms for which they desire treatment. Some experts believe that if the patient is incorrectly diagnosed with major depressive disorder for which antidepressants are prescribed, antidepressants can precipitate the emergence of hypomanic or manic symptoms.[40] Others argue that any such risk is more likely to be associated with older antidepressants, notably tricyclic antidepressants, than with selective serotonin reuptake inhibitors (SSRIs), but neither are SSRIs very effective for treating the depression associated with bipolar disorder.[17]

Treatment of patients with schizoaffective disorder is hindered by a lack of guidelines,[41] which may stem from a dearth of studies addressing the schizoaffective population per se, instead of evaluating a mixture of schizoaffective and schizophrenia patients.[12] Studies identifying genetic combinations associated with brain structure and function could facilitate the development of diagnoses that are more useful in research and clinical practice.

Increased clinical contact. In a study discussed above,[25] the authors speculated that a reason for low relapse rates (37 percent overall) in their study may have been the frequency of clinical contact — every two weeks — during the study, which is much more often than would occur in routine practice. During these visits, risperidone LAI subjects were given their injections while the oral SGA subjects were given their antipsychotic medications (thus sparing them a trip to a pharmacy to fill the prescription), which were provided by the manufacturers cost-free. In addition, adherence was assessed during these visits and reminders were sent to patients who missed a visit. All these features may have promoted better adherence and affected the results. In addition, documented nonadherence was not an entry criterion. Further, the subjects enrolled in this study may have been less likely to become nonadherent to oral antipsychotics because of their greater engagement with their own health care, as evidenced by their decision to enroll in the study in the first place.

Patients who have elected Zyprexa Relprevv as their LAI could be provided with additional meaningful clinical contact if health care providers take advantage of the three-hour observation period (discussed above) to engage patients in discussions about coping with their disorder and related conditions.

Economic analyses. A study discussed above estimated the economic burden of schizophrenia in the United States.[16] An updated study presumably would show a substantial increase in the amount spent for direct health care costs and a shift in the percentages allocated to each component (e.g., outpatient care, inpatient care).

In another study mentioned above,[15] the authors estimated 12-month prevalence by type of insurance coverage in 2002. An update of this study would be timely and presumably would find changes in insurance coverage prevalence patterns stemming from implementation of the Affordable Care Act.

In addition, a retrospective claims analysis was discussed above showing that patients receiving monthly LAI paliperidone had lower health care utilization and costs than patients treated with oral atypical antipsychotics over a 12-month period.[29] If the VHA database contains sufficient data about the use of other LAIs, including inexpensive first-generation LAIs, a study using similar methodology to compare a greater number of LAIs with oral antipsychotics might provide important insights with financial implications for health plans.

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Biosimilars — Overcoming Challenges to Ensure Cost-Effective Care

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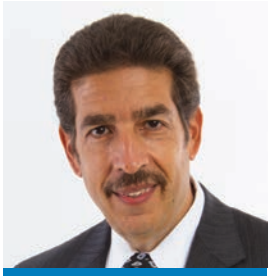
In 1984, generic drugs entered the United States (US) marketplace for the first time.[1] In 2014 approximately 3.8 billion of the 4.3 billion prescriptions dispensed in the US were filled with generic drugs, accounting for nearly nine out of every 10 prescriptions dispensed in the US, and $254 billion in savings. Generic drugs accounted for a total, over the past 10 years, of $1.68 trillion in sales.[2] In 2015 the US had its first opportunity to provide patients with access to biosimilars, a newly available category of drugs. Like generics, biosimilars are projected to generate significant health care savings; however, realizing these savings and maximizing the financial impact of these agents requires the coordinated uptake and acceptance of biosimilars by stakeholders in the U.S. health care system.

Biosimilars are biologic medications recognized as being as safe and effective as the originator, or reference product they are modeled after. As they become available, biosimilars will face the challenges of being integrated into the U.S. health care system, with new regulatory systems and uptake hurdles ahead. In contrast, Europe created a legal framework for biosimilars in 2003 and developed official guidelines in 2005.[3] Since January 2016, Europe has approved 22 biosimilar drugs, based on eight reference products.[4] In this respect, the European and U.S. markets vary widely in their uptake and experience with managing biosimilars. In Europe, the adoption of a biosimilar varies by country, cost, and use, depending on site of care (SOC). As more biosimilars enter the U.S. market, stakeholders will be tasked with making decisions surrounding the adoption and management of biosimilar access, pricing, and approval methodology. Each of these are factors influencing biosimilar acceptance and utilization.

The US has taken a more cautious approach in the approval and uptake of biosimilar medications, and the Food and Drug Administration (FDA) has not issued guidance on how interchangeability will be determined. As a result, there are currently no FDA-approved interchangeable biosimilars in the US.[5] On March 6, 2015, the first biosimilar was approved by the FDA under the Biologics Price Competition and Innovation Act (BPCIA). Filgrastim-sndz (Zarxio®), manufactured by Sandoz, is a biosimilar version of filgrastim (Neupogen®, Amgen), an injectable granulocyte colony-stimulating factor (G-CSF).[6] It is important to note that Zarxio was approved for all five indications for which Neupogen is approved. Before launch, analysts projected that Zarxio would be 30 percent cheaper than Neupogen and contribute up to $6 billion in health care system savings within a decade of approval.[2] However, Zarxio's original wholesale acquisition cost (WAC) was listed as 15 percent less than the WAC of Neupogen, significantly decreasing the savings potential associated with this first to market biosimilar agent.[7] On April 5, 2016, the FDA approved Celltrion/Pfizer's Inflectra™ (infliximab-dyyb), a biosimilar to Janssen Biotech Inc.'s Remicade (infliximab) for treatment of autoimmune diseases, making Inflectra the second biosimilar to be approved.[8] With these approvals, the stage has been set for biosimilar utilization, with additional anticipated growth and savings opportunities in the United States, as six other biosimilar applications having been accepted by the FDA.[9] However, managed care experience demonstrating the cost-savings impact of biosimilars for payor organizations in the US is not available to date.



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Education Is Key

The uptake of biosimilar therapies and the realization of potential savings through the appropriate use of these therapies requires the education of health care stakeholders. First, patients and prescribers must have confidence in the clinical value of these therapies. At a minimum, this requires comprehensive education and understanding of the role, usage, and opportunities associated with biosimilar agents. A recently conducted survey of nearly 300 primary care physicians (PCPs) and specialists concluded that while 94 percent of providers viewed biosimilar agents as providing health care value, they lacked the education to strongly support their utilization.[10] Prescribers viewed the benefits of biosimilars as offering:[10]

"Lower costs to patients/the health system" (35 percent)

"Greater patient access to therapies" (30 percent)

"Increased choice among prescribing options" (27 percent)

When questioned about how likely they were to prescribe biosimilar agents, 17 percent of physicians viewed themselves as being very likely to prescribe biosimilars, 70 percent reported they were unsure, or somewhat likely to prescribe them, while the remaining 13 percent of respondents indicated they were unlikely to prescribe biosimilar drugs.[10] Survey participants identified trusted sources of information to support their education and potential uptake of these new therapies as including specialty societies (25 percent), peers (19 percent), and insights shared by key opinion leaders (KOLs) (18 percent).[10]

Significant opportunities exist for improving provider understanding of biosimilars and addressing barriers to their uptake. First, there is a need for education of providers regarding the clinical role and value of biosimilars, as well as the financial and reimbursement implications of prescribing these agents. Although it's generally understood that providers will view FDA-approved biosimilar products as equivalent to the reference product, it's possible some prescribers may utilize these agents with caution. Payors can serve a valuable role in addressing the educational deficit regarding biosimilars, and support efforts to enhance prescriber understanding of the role in therapy and the benefits of biosimilar agents.

Promoting Patient Acceptance

Likewise, patient acceptance and understanding of the role of biosimilar agents is critical. As providers face a multitude of time demands and resource limitations, payor support in helping them to address the challenges of properly educating patients regarding the role of biosimilar drugs will be highly valuable. Specifically, payors can provide or support patient education efforts. In addition to education, financial support of patients will be essential to encourage biosimilar uptake. To be viewed as beneficial to patients, financial and clinical support programs offered by biosimilar manufacturers will need to meet or exceed those offered by the reference product manufacturer.

Educational efforts should help patients and providers in understanding manufacturing processes associated with biosimilars, sharing the information in a manner that clarifies that while these processes preclude production of "identical" molecules to the reference product, the biosimilar will not have any clinically meaningful differences from the reference product. This discussion raises the question of how payors and providers will handle situations in which the biosimilar does not have FDA-approved labeling for use in all of the indications for which the reference drug is indicated. Prescribers must have an understanding of the concept of extrapolation of indications, and payors will be tasked with defining a strategy for accepting or not accepting extrapolated indications. The determination of how extrapolated indications will be handled by providers and payors is expected to influence the uptake of biosimilars and the extent to which the savings potential of these agents is realized.

In order for payors to realize the savings biosimilars are projected to offer, they will be tasked with supporting biosimilar utilization, which will include meeting provider educational needs, as discussed above. This will likely involve utilizing manufacturer resources around reimbursement, indications for use, the manufacturing process, etc. Additionally, realizing biosimilar savings will require providers to be equipped to offer patients an appropriate level of education and support. Payor biosimilar management strategies will include determining the target audience for use of biosimilars; whether these agents should be utilized in new patients with acute or chronic treatment needs, or as a replacement of ongoing therapy in long-term treatment of chronic conditions. Patients being migrated from an existing treatment regimen, of the reference product, may be resistant to this change of therapy. These modifications can only be undertaken successfully when providers are sufficiently confident to educate patients regarding the implications of making treatment changes.

Prescriber confidence is essential in navigating the uptake and appropriate utilization of biosimilars. Over the past several years prescribers have had numerous experiences with prescription drug shortages and the impact of these outages on drug therapy — as they may adversely affect treatment, result in compromised or delayed medical procedures, or may contribute to medication errors. This may be front of mind with prescribers as medication shortages currently exist within the traditional drug channel, with the FDA acknowledging that in 2015, there were many drugs in short supply.[11]

The challenges with uptake of biosimilars are not limited to provider acceptance. Payors are tasked with developing medical policies that permit access to biosimilars and encourage provider confidence that the use of biosimilars will not result in adverse financial outcomes for their practice and that they will be appropriately reimbursed. This is an important aspect of biosimilar uptake as financial education is essential. To be beneficial for providers considering the use of biosimilars, financial education should include a review of Medicare Part B benefit strategies, and help providers to understand that a reimbursement methodology based on the average sales price (ASP) of the biosimilar plus 6 percent of the ASP of the reference product has been developed as a means of removing financial incentives to prescribe one product over another.[12] (Note: A 2 percent decrease in Part B drug reimbursement by the Centers for Medicare & Medicaid Services [CMS], enacted as a result of the 2012 budget sequester and extended in 2014, has reduced this markup through 2024.[13] For example, as a result of this decision, providers are now reimbursed for oncolytics at ASP plus 4.3 percent.[13])

Coding for Billing

With this as background, billing for biosimilar agents requires the explicit attention of payors and providers. CMS has indicated that biosimilars for the same reference product will share the same Healthcare Common Procedure Coding System (HCPCS) code, and the reference product will retain a unique code.[14] Claims for biosimilars will require a modifier, identifying the manufacturer of the biosimilar, and helping payors to identify specific biosimilar product claims. CMS may issue HCPCS codes for biosimilars in addition to the previously mentioned modifiers. There are a couple of nuances for prescribers around biosimilar coding. First, if the HCPCS and modifier do not appear on CMS's quarterly update — notifying providers of billing and coding changes — then use of the modifier is not required. In the absence of an HCPCS code that can describe biosimilars that are new to the market, providers can bill with a miscellaneous or "not otherwise classified" code. When a miscellaneous code is utilized

modifier codes are not required. It's important to note that the reimbursement amount for a biosimilar is not influenced by the use of a modifier.[14]

This preceding coding discussion demonstrates the complexity associated with biosimilar uptake, and the importance of coordinated payor and provider communication and education in avoiding coverage and reimbursement errors or unnecessary issues with reimbursement of providers. Incurring a delay or confusion in billing of biosimilars is a challenge that might interfere with provider uptake of biosimilars. To avoid unnecessary challenges to biosimilar uptake, payors may consider implementing the following strategies:

- Create a provider-facing biosimilar portal to facilitate ease of billing and reduce billing and coding errors
- Implement a payor-sponsored campaign to provide updates, training, and billing and coding support
- Develop proactive strategies to remove biosimilar uptake barriers, streamlining the administrative process and assuring timely and accurate payment for biosimilars
- Partner with manufacturers to utilize educational resources supporting appropriate use of biosimilars, including medical policies and benefit management strategies such as prior authorization, fee schedule management, or other product and plan appropriate strategies
- Develop and implement policies that are clear, relevant, and support the coordinated management of and utilization of biosimilars in a clinically and economically appropriate manner

Payors should consider the importance of creating shared payor and provider cost savings, as it's anticipated that biosimilar adoption will offer a meaningful savings opportunity, potentially reducing specialty drug spending. This being said, biosimilar drugs are costly and the realization of savings will depend upon the timing of each entrant to market, and the uptake of each product. Payors will be challenged to manage new biosimilar entrants in a manner that accounts for loss of rebates typically provided by manufacturers of reference products. These rebate reductions must be considered in conjunction with payor strategies to incentivize prescriber use of biosimilar products. Biosimilar uptake initiatives must include a mechanism that provides adequate reimbursement for physicians.

The Complexities of Estimating Savings

With this as background, it is reasonable that estimating potential cost savings associated with biosimilars involves many factors, and there is no consensus regarding how these scenarios will play out financially. Express Scripts predicted savings of up to $250 billion between 2014 and 2024, corresponding to the introduction and uptake of 11 biosimilars.[15] Rand Corporation estimated a $44.2 billion decrease in spending on biologics for the same time frame, approximately 4 percent of total spending on biologics.[16] The United States Congressional Budget Office (CBO) projected a $25 billion reduction in total prescription drug spending associated with biosimilar utilization from 2009 to 2018, equivalent to a 0.5 percent reduction for that 10-year period.[17]

Meanwhile, Milliman offered three different biosimilar savings scenarios based on a 10,000 member commercial health plan. Savings to employers were projected as ranging from over $217,000 to nearly $636,000 for 2019.[18] These savings would represent 2.6 to 7.6 percent of prescription drug spending and 0.3 to 0.8 percent of total health care spending.[18] The savings were abstracted from market penetration scenarios as follows:[18]

Scenario one: aggressive market penetration (30 percent) — representing complete patient/physician acceptance (30 percent discount, and a $50 copay differential)

Scenario two: moderate market uptake with 15 percent penetration, with half of patients and physicians accepting biosimilar usage (20 percent price discount, and $50 copay differential)

Scenario three: market penetration ranging from 15 to 25 percent (price discount of 20 to 30 percent with gradual growth during the five years post-approval)

As demonstrated in the preceding discussion, the realization of savings through biosimilar uptake is a complex scenario played out through pricing, rebates, and patient and provider acceptance, as well as payor policies. Payors will be tasked with carefully assessing the financial implications of promoting biosimilar utilization, considering the previously explored costs, and rebate scenarios associated with reference and biosimilar agents while encouraging utilization of biosimilars.

One of the main factors influencing biosimilar utilization is the motivation providers will have to utilize these agents. Payors may consider implementing a shared savings program in association with biosimilars for providers. This might include increasing reimbursement to prescribers of biosimilar products, and creating a mechanism for physician practices and infusion centers to realize some of the savings associated with biosimilar utilization through shared savings programs. Accountable Care Organizations (ACOs) are a health care delivery sites perfectly positioned to optimize the savings potential associated with biosimilars, equipped to share savings while optimizing patient care.

Biosimilars are entrants into a prescription drug segment that has historically involved minimal competition among products. The introduction of biosimilars creates a unique opportunity to offer choice, and savings. As additional biosimilar therapies enter the market, the potential for a competitive environment capable of driving savings develops.

Implications for Payors

The financial management of these therapies will require payors to develop innovative and thoughtful strategies. The dynamics of the biosimilar segment are crucial, in part due to the pricing scenarios playing out with the first biosimilar entrants. For example, as of Q1 2016 there was only a 3.8 percent difference between the ASP of Zarxio and Neupogen.[19,20] If this narrow difference remains the case, the balance of clinical and financial considerations, including rebates and savings incentives, must be considered carefully and comprehensively by payors implementing programs intended to drive biosimilar utilization.

In developing biosimilar management strategies, payors can proactively engage with providers, including large group practices and hospital systems to coordinate efforts and improve collaboration. Likewise, payors should consider information technology (IT) infrastructure needs and anticipate necessary modification that may be required to facilitate the processing of biosimilars, including approval, billing and coding, and reimbursement processes. These efforts are critical to supporting biosimilar uptake in a manner consistent with payor strategies; however, they must align with physician prescribing patterns and practice operations. These initiatives will require a coordinated effort between payors and providers, not only with regard to systems and processes, but also alignment around incentive programs such as shared savings and other strategies to promote the appropriate utilization of lower cost biosimilar alternatives.

The responsibilities that fall upon payors in managing the uptake of biosimilars have a corresponding accountability that lies with biosimilar manufacturers. Of course manufacturers of biosimilar products must develop sound financial strategies for supporting product uptake, giving consideration to pricing implications for all stake holders — payors, providers, and patients. As these products make their way to the market, it is incumbent upon manufacturers to provide guidance surrounding the use of biosimilars; naming, extrapolation of indications, and interchangeability. Manufacturer support and education of stakeholders is critical, including financial arrangements, clinical education and patient and provider support resources. Sound clinical and scientific support must be provided to all health care stakeholders to support the prescribing and appropriate use of these therapies. This may include, for example, anticipating circumstances in which a biosimilar is not indicated for each indication for which the reference product has been FDA approved. Resources, including clinical trials and sound scientific evidence must be made available.

Clearly the biosimilar market offers an opportunity for all health care stakeholders, payors, providers, and patients. The appeal of cost savings is real and speaks to the interests of the health care system as a whole. Realizing savings associated with biosimilars requires planning, collaboration, and coordination. In the absence of aligning strategies with consideration of the interests of payors, providers and patients, there will be challenges to uptake which will adversely impact biosimilar uptake and the realization of cost savings. Prescribers asked to prescribe biosimilars must be adequately educated, supported with seamlessly integrated payor policies, and reimbursement systems that protect their financial interests. Payors must partner with biosimilar manufacturers in a manner that supports these efforts. Biosimilar manufacturers must support payors, providers, and patients financially and in terms of education. Clearly, there is a need for mutually beneficial collaboration to promote the successful adoption of biosimilar therapies as the health care industry embarks upon an era in which the appropriate use of these therapies offers savings opportunities for the health care system.

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Value-Based PBM — Implications for Various Stakeholders

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Value is more than a buzzword among health care stakeholders, but stakeholders — payors, providers, patients, and pharmaceutical manufacturers — define value differently, based on their needs, obligations, and roles within the evolving health care and managed care paradigm. Each stakeholder, while looking out for its unique interests, must also consider how its priorities, perspectives, and business model affect the others — their counterparts, and in some cases, partners. Payors are a common thread intertwined within this continuum of health care services, interfacing with each stakeholder in a significant, although different manner. As they navigate the changing managed health care marketplace, payors must proceed in a manner that protects their interests, even as they give consideration to the impact their strategies and initiatives may have internally and upon other health care stakeholders. One unique opportunity for payors exists within the management of prescription drug utilization, specifically in assessing and refining expectations surrounding their Pharmacy Benefit Management (PBM) services and relationships, and how these translate into value for payors and ultimately, all health care stakeholders.

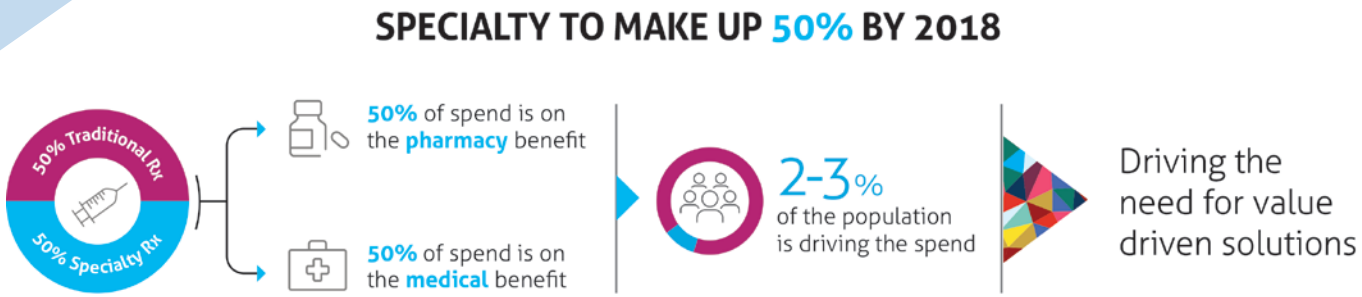
Historically, measures of success in the PBM industry focused on leveraging volume as a means of managing drug costs. PBMs demonstrated value by offering what are now considered standard, or core, services. Typically these offerings consist of claim adjudication, utilization management, mail order, customer service, some clinical support services, and of course, financial support in the form of volume-driven rebates and discounts. Times have changed as the Accountable Care Act (ACA), increasing government regulation, rising drug prices, and growing availability and demand for specialty pharmacy drug products have profoundly impacted the use, costs, and management of prescription drug therapies within the managed health care marketplace.

Accordingly, expectations surrounding prescription drug benefit management among stakeholders have been, and will continue to be, profoundly impacted by the shifting health care environment. Specifically, as payors seek to provide patient or member support, access to care, and expanded services, while maintaining profitability, they are reassessing business models and relationships. For payors, this includes taking a close look at the manner in which prescription drugs are managed, giving consideration to the clinical and financial impact of specialty drug spending, in particular. In response, payors are increasingly looking to PBMs to refine their services, with an eye toward driving outcomes. It is no longer sufficient for a PBM to provide products at a discounted price. Essentially, payors are looking for PBMs to provide "value over volume."

Challenges Facing PBMs

This evolution in payor expectations of PBMs is highly driven by the pressures of rising prescription drug costs — particularly specialty drug spending. Make no mistake about it, volume-based savings remain a significant facet of PBM and payor relationships, but they are no longer the key financial objective of payor-PBM agreements, as they once were.

PBMs are now challenged to stretch beyond their traditional scope of offerings to provide the services payors expect — they are tasked with providing and demonstrating value. What is value and how is it defined in



the PBM-payor relationship? First and foremost, PBM-payor relationships moving forward must be partnerships in order to successfully navigate these formerly uncharted waters. It's not sufficient for a PBM to provide expanded services, such as clinical programs, in name only. Successful implementation of these initiatives will require tomorrow's successful value-based PBMs to have an innovative culture, a modular and flexible service model, and a platform utilizing leading-edge technology. PBMs capable of providing adequate support to payor partners must actively integrate and apply clinical expertise into programs that support improved patient outcomes and consider patients comprehensively, while giving appropriate consideration of unique patient needs — and offering comprehensive solutions, which may include unique program components, such as integrating behavioral health support as warranted.

Clearly, the PBM of the future must have a new orientation — no longer focused exclusively on volume-based strategies. Tomorrow's value-based PBM must provide value by looking beyond the current silos that commonly focus upon pharmacy drug benefit approaches that apply "traditional" utilization management strategies (step therapy, prior authorization, etc.) to maximize rebates and manage prescription drug spending. Effective management of the future must bridge the management of prescription therapies, particularly specialty drugs, via either the medical or pharmacy benefit. Applying innovative strategies to optimize management of the use of and administration of prescription drugs through whichever benefit, medical or pharmacy, the therapy that is processed will be an essential attribute of PBMs' demonstrating value to payor partners. Focus upon coordination of specialty drug management through both the pharmacy and medical pharmacy benefits will only gain importance as the availability, costs, and utilization of expensive specialty therapies rises, as acceleration of specialty drug utilization is projected.

These current and anticipated shifts in the clinical and economic landscape will drive the challenges and amplify the financial importance of managing medical pharmacy spend. PBMs providing value will do so by offering comprehensive prescription drug management support for payors, across the benefit design, with particular attention to effectively managing drug utilization and spending within the medical benefit arm of the organization. As an example, Magellan Rx Management has focused on developing patient and provider engagement strategies, and employing advanced analytics and comprehensive specialty drug management programs for both the medical and pharmacy benefit.

Interpreting Data Is Key

This application of advanced analytics is integral to the service and offerings of the value-based PBM of the future. It is insufficient to simply capture and possess data. Going to the next level, the ability to analyze and report data, while beneficial, falls short of having a demonstrable clinical and economic impact. Data capture and reporting alone are inadequate as a means of providing value to payors if this data is not properly evaluated, interpreted, and then integrated into effective clinical management strategies. These identified strategies must be capable of serving as a platform for significant clinical improvement and development of cutting-edge programs that enhance care and manage costs, across both the medical and pharmacy components of the benefit. PBMs with an eye to the future are those capable of:

- Providing rigorous analytical support to payor data in order to help payors identify opportunities to improve outcomes, while realizing savings
- Collaboration to ensure providers have information needed to optimize treatment — promoting access to and use of the most efficacious and cost-effective drugs
- Enhanced customer-facing strategies to increase member understanding and effective utilization of pharmacy and medical benefit therapies

With data management capabilities as a cornerstone, the value-based PBM is poised to assess payor data, applying predictive analytics as appropriate to conduct a robust and meaningful cross-functional analysis of costs, utilization of therapies, and outcomes. A well-constructed and executed analysis supports both the financial and clinical objectives of the payor — financially supporting cost management while simultaneously creating an opportunity to identify and address existing or emerging gaps in care. As a result of these analyses, payors will be poised to support providers, provider groups, hospitals, outpatient treatment facilities, and other partners, such as accountable care organizations (ACOs) by providing feedback regarding current clinical and economic opportunities to improve outcomes and manage costs — ultimately benefiting the patient. As one dimension of these analyses, value-based PBMs can support payors in developing targeted initiatives that address identified gaps in care. For example, programs may be developed to improve member adherence with therapy and the selection of the most clinically appropriate treatment, as they simultaneously support payor objectives, such as improving the identification,

recognition, and understanding of opportunities for managing trend drivers and helping to identify other areas of concern or opportunities to improve care.

With the support of value-based PBM, payors have the opportunity to expand specialty drug management capabilities, developing new clinical programs for specific disease states, with the ability to target diseases that are highly significant for each organization, either due to cost, clinical relevance, prevalence, or demonstrated gaps in care. Some examples of programs with such experience that exist within Magellan Rx Management include the clinical programs to guide the treatment of age-related macular degeneration, hepatitis C, and chronic myelogenous leukemia (CML). These programs might include clinical interventions, product preferencing, and targeted clinical patient and provider support programs.

A Case in Point

For a large regional health plan, representing about 1 million commercial lives, Magellan Rx Management partnered to offer medical formulary management programs in the following areas:

- Viscosupplementation
- Botulinum toxins
- Contraceptives
- Gaucher's disease

Magellan also worked with this payor to implement a variable reimbursement fee schedule, with a maximum allowable cost (MAC)/least cost alternative (LCA) product selection strategy. A proprietary methodology was applied to promote generic utilization and equalize margins on products within several therapeutic classes, including intravenous immunoglobulin (IVIG), taxanes, folinic acids, ophthalmic injections, viscosupplementation, and antiemetics. Savings in the antiemetic category alone have exceeded $3.5 million since the program's inception in 2010, by removing incentives for physicians to prescribe higher-cost, branded antiemetics, rather than the low-cost preferred alternatives.

Additionally, value-based PBMs are equipped to support payors in the development and implementation of unique initiatives, such as site of care management programs. These programs create an opportunity to administer initiatives focused on oversight and management of the treatment and administration location for certain high-cost therapies, typically administered at either a provider office or an alternative administration site such as a hospital outpatient administration facility. By encouraging the use of the most clinically, therapeutically and financially cost-effective therapy, site of care management programs offer a means of assuring treatment is administered in the most clinically and financially appropriate setting. As an example of success in this area, Magellan Rx Management's site of service netted over $1 million in savings for two regional health plans in a six-month period. The program, which also received positive feedback from patients, demonstrated the possibilities such programs have to generate savings, while improving patient access to care. Characterized as a solution that places the patient first, the program was overseen by a collaborative team of health care professionals, including nurses, pharmacists, and physicians.[1]

Innovative strategies, such as outcomes-based contracting, are another means by which value-based PBMs further support payor objectives. Outcomes-based contracts are a unique and customized partnership opportunity that considers stakeholder interests by giving consideration to payor-specific data, supported by robust analytics to define opportunities for optimizing clinical and economic outcomes in the best interest of all stakeholders.

Additionally, value-based PBMs can assist payors in the identification of gaps, and the development and implementation of cutting edge and customized clinical programs designed to improve STAR ratings and HEDIS measures. Such programs are relevant and valuable to payors, as they support clinical initiatives, assisting payors in meeting objectives that translate into financial benefits for the organization.

In light of specialty drug trends, such as a burgeoning pharmaceutical pipeline — dominated by specialty drugs that are estimated to comprise 50 percent of overall drug spend by 2018,[2] payors are changing their view of essential PBM support services. Forward-thinking payors are seeking the support of a value-based PBM with expertise in management of complex and costly therapies, including specialty drugs administered within the medical benefit. With a decade of experience in this arena, Magellan Rx Management is one example of a full-service PBM with the distinction of having significant expertise in managing specialty drugs, including those covered under the medical benefit. The additional benefit of clinical expertise and robust analytical support are critical in the development of cutting edge clinical programs that simultaneously support the objectives of payors and consider the interests of other stakeholders in the managed care marketplace. These are critical strengths that value-based PBMs of the future must possess in order to effectively support payors in meeting the demands of tomorrow's health care marketplace; providing tailor-made, disease-specific services that provide value and drive healthier outcomes for members.

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For Your Patients With IBS-D

Does the Threat of Diarrhea and Abdominal Pain Keep Looming?

VIBERZI targets the core components of IBS-D, diarrhea and abdominal pain, helping provide lasting relief*

*VIBERZI was studied in two placebo-controlled, Phase 3 trials in >2400 IBS-D adult patients (aged 18-80). A responder was defined as a patient with ≥30% reduction in abdominal pain AND improvement in stool consistency to <5 on the Bristol Stool Scale on at least 50% of days throughout 12 and 26 weeks. Improvement in abdominal pain in the absence of a bowel movement was also considered a response day. The proportion of patients who were combined responders to VIBERZI at each 4-week interval was numerically higher than placebo as early as month 1 through month 6.

Indication

VIBERZI is indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

Important Safety Information

Contraindications

- Known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction; a history of pancreatitis; structural diseases of the pancreas.
- Alcoholism, alcohol abuse, alcohol addiction, or drink more than 3 alcoholic beverages per day.
- Severe hepatic impairment.
- A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction.

Warnings and Precautions

Sphincter of Oddi Spasm:

- There is a potential for increased risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain (eg, biliary-type pain) with VIBERZI. These events were reported in less than 1% of patients receiving VIBERZI in clinical trials.
- Patients without a gallbladder are at increased risk. Consider alternative therapies before using VIBERZI in patients without a gallbladder and evaluate the benefits and risks of VIBERZI in these patients.

Please see additional Important Safety Information and brief summary of full Prescribing Information on following pages.

Viberzi™
(eluxadoline) tablets C IV
75 mg • 100 mg

Be Proactive Against IBS-D

VIBERZI: Lasting Relief of Diarrhea and Abdominal Pain*

VIBERZI binds to opioid receptors in the gut, which may play a key role in controlling GI motility and visceral hypersensitivity

- Based on nonclinical data

VIBERZI provides sustained efficacy against diarrhea and abdominal pain

- The proportion of patients who were combined responders to VIBERZI at each 4-week interval was numerically higher than placebo as early as month 1 through month 6*

VIBERZI has a well-established safety profile from trials lasting up to 1 year

*A responder was defined as a patient with ≥30% reduction in abdominal pain AND improvement in stool consistency to <5 on the Bristol Stool Scale on at least 50% of days throughout 12 and 26 weeks. Improvement in abdominal pain in the absence of a bowel movement was also considered a response day.

Important Safety Information

Warnings and Precautions (continued)

Sphincter of Oddi Spasm (continued):

- Inform patients without a gallbladder that they may be at increased risk for symptoms of sphincter of Oddi spasm, such as elevated liver transaminases associated with abdominal pain or pancreatitis, especially during the first few weeks of treatment. Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms of sphincter of Oddi spasm.

Pancreatitis:

- There is a potential for increased risk of pancreatitis not associated with sphincter of Oddi spasm; such events were reported in less than 1% of patients receiving VIBERZI in clinical trials, and the majority were associated with excessive alcohol intake. All pancreatic events resolved upon discontinuation of VIBERZI.
- Instruct patients to avoid chronic or acute excessive alcohol use while taking VIBERZI. Monitor for new or worsening abdominal pain that may radiate to the back or shoulder, with or without nausea and vomiting, associated with elevations of pancreatic enzymes. Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms suggestive of pancreatitis.

Adverse Reactions

- The most commonly reported adverse reactions (incidence >5% and greater than placebo) were constipation, nausea, and abdominal pain.

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

Visit ViberziHCP.com to learn more

Viberzi™
(eluxadoline) tablets C IV
75 mg • 100 mg

Be Proactive Against IBS-D

Allergan

VIBERZI (eluxadoline) tablets, for oral use, CIV
Brief Summary of full Prescribing Information
Initial U.S. Approval: 2015

INDICATIONS AND USAGE: VIBERZI is indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

CONTRAINDICATIONS: VIBERZI is contraindicated in patients with: Known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction. These patients are at increased risk for sphincter of Oddi spasm *[see Warnings and Precautions]*; Alcoholism, alcohol abuse or alcohol addiction, or in patients who drink more than 3 alcoholic beverages per day. These patients are at increased risk for acute pancreatitis *[see Warnings and Precautions]*; A history of pancreatitis; or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction. These patients are at increased risk for acute pancreatitis *[see Warnings and Precautions]*; Severe hepatic impairment (Child-Pugh Class C). These patients are at risk for significantly increased plasma concentrations of eluxadoline *[see Use in Specific Populations]*; A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction. These patients may be at risk for severe complications of bowel obstruction.

WARNINGS AND PRECAUTIONS: Sphincter of Oddi Spasm - Given the mu-opioid receptor agonism of VIBERZI, there is a potential for increased risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain (e.g., biliary-type pain) with VIBERZI. In clinical trials, sphincter of Oddi spasm occurred in less than 1% of patients receiving VIBERZI. The majority of these patients presented within the first week of treatment and the event resolved on discontinuation of VIBERZI. Patients without a gallbladder are at increased risk *[see Adverse Reactions]*. Consider alternative therapies before using VIBERZI in patients without a gallbladder and evaluate the benefits and risks of VIBERZI in these patients in the context of their symptom severity. The recommended dosage of VIBERZI is 75 mg twice daily in patients without a gallbladder *[see Dosage and Administration in full Prescribing Information]*. If VIBERZI is used in such a patient, inform them that they may be at increased risk for adverse reactions and monitor them for symptoms of sphincter of Oddi spasm, such as elevated liver transaminases associated with abdominal pain or pancreatitis, especially during the first few weeks of treatment. Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms suggestive of sphincter of Oddi spasm such as acute worsening of abdominal pain, (e.g., acute epigastric or biliary [i.e., right upper quadrant] pain), that may radiate to the back or shoulder with or without nausea and vomiting, associated with elevations of pancreatic enzymes or liver transaminases. Do not restart VIBERZI in patients who developed biliary duct obstruction or sphincter of Oddi spasm while taking VIBERZI *[see Contraindications]*. **Pancreatitis -** There is a potential for increased risk of pancreatitis, not associated with sphincter of Oddi spasm, when taking VIBERZI. Additional cases of pancreatitis, not associated with sphincter of Oddi spasm, were reported in less than 1% of patients receiving VIBERZI in clinical trials. The majority were associated with excessive alcohol intake. All pancreatic events, whether or not associated with sphincter of Oddi spasm, resolved upon discontinuation of VIBERZI; patients did not have organ failure or local or systemic complications *[see Adverse Reactions]*. Instruct patients to avoid chronic or acute excessive alcohol use while taking VIBERZI. Monitor for new or worsening abdominal pain that may radiate to the back or shoulder, with or without nausea and vomiting. Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms suggestive of pancreatitis such as acute abdominal or epigastric pain radiating to the back associated with elevations of pancreatic enzymes *[see Contraindications]*.

ADVERSE REACTIONS: The following adverse reactions described below and elsewhere in the labeling include: Sphincter of Oddi Spasm *[see Warnings and Precautions]*; Pancreatitis *[see Warnings and Precautions]*. **Clinical Trials Experience -** Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Over 1700 patients with IBS-D have been treated with 75 or 100 mg of VIBERZI twice daily in controlled trials. Exposures from placebo-controlled clinical trials in adult patients with IBS-D included 1391 exposed for 3 months, 1001 exposed for 6 months and 488 exposed for one year. Demographic characteristics were comparable between the treatment groups *[see Clinical Studies in full Prescribing Information]*. Data described below represent pooled data compared to placebo across the randomized trials. *Sphincter of Oddi Spasm* - In clinical trials, sphincter of Oddi spasm occurred in 0.2% (2/807) of patients receiving 75 mg and 0.8% (8/1032) of patients receiving 100 mg VIBERZI twice daily. Among patients receiving 75 mg, 1/807 (0.1%) patient experienced a sphincter of Oddi spasm presenting with abdominal pain but with lipase elevation less than 3 times the upper limit of normal (ULN) and 1/ 807 (0.1%) patient experienced a sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain; Among patients receiving 100 mg, 1/1032 (0.1%) patient experienced a sphincter of Oddi spasm manifested as pancreatitis and 7/1032 (0.7%) patients experienced sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain. In patients without a gallbladder, 2/165 (1.2%) and 8/184 (4.3%) of patients receiving 75 mg and 100 mg, respectively, experienced a sphincter of Oddi spasm vs 0/1317 (0%) in patients with a gallbladder who had received either 75 mg or 100 mg treatment. Of those patients who experienced a sphincter of Oddi spasm, 80% (8/10) reported their first onset of symptoms within the first week of treatment. The case of sphincter of Oddi spasm-induced pancreatitis occurred within minutes of taking the first dose of VIBERZI. No cases of sphincter of Oddi spasm occurred greater than 1 month after treatment onset. All events resolved upon discontinuation of VIBERZI, with symptoms typically improved by the following day. *Pancreatitis* - Additional cases of pancreatitis, not associated with sphincter of Oddi spasm, were reported in 2/807 (0.2%) of patients receiving 75 mg and 3/1032 (0.3%) of patients receiving 100 mg VIBERZI twice daily in clinical trials. Of these 5 cases, 3 were associated with excessive alcohol intake, one was associated with biliary sludge, and in one case the patient discontinued VIBERZI 2 weeks prior to the onset of symptoms. All pancreatic events resolved with lipase normalization upon discontinuation of VIBERZI, with 80% (4/5) resolving within 1 week of treatment discontinuation. The case of sphincter of Oddi spasm-induced pancreatitis resolved within 24 hours of discontinuation. *Common Adverse Reactions* - **Table 1** provides the incidence of common* adverse reactions reported in > 2% of IBS-D patients in either VIBERZI treatment group and at an incidence greater than in the placebo group. Values are shown in parentheses as VIBERZI 100 mg twice daily (N=1032), VIBERZI 75 mg twice daily (N=807), and Placebo (N=975). Constipation (8, 7, 2); Nausea (7, 8, 5); Abdominal Pain** (7, 6, 4); Upper Respiratory Tract Infection (5, 3, 4); Vomiting (4, 4, 1); Nasopharyngitis (3, 4, 3); Abdominal Distention (3, 3, 2); Bronchitis (3, 3, 2); Dizziness (3, 3, 2); Flatulence (3, 3, 2); Rash*** (3, 3, 2); Increased ALT (3, 2, 1); Fatigue (2, 3, 2); Viral gastroenteritis (1, 3, 2).
* Reported in > 2% of VIBERZI-treated patients at either dose and at an incidence greater than in placebo-treated patients ** "Abdominal Pain" term includes: abdominal pain, abdominal pain lower, and abdominal pain upper *** "Rash" term includes: dermatitis, dermatitis allergic, rash, rash erythematous, rash generalized, rash maculo-papular, rash papular, rash pruritic, urticaria, and idiopathic urticaria. Constipation was the most commonly reported adverse reaction in VIBERZI-treated patients in these trials. Approximately 50% of constipation events occurred within the first 2 weeks of treatment while the majority occurred within the first 3 months of therapy. Rates of severe constipation were less than 1% in patients receiving 75 mg and 100 mg VIBERZI. Similar rates of constipation occurred between the active and placebo arms beyond 3 months of treatment. *Adverse Reactions Leading to Discontinuation* - Eight percent of patients treated with 75 mg, 8% of patients treated with 100 mg VIBERZI and 4% of patients treated with placebo discontinued prematurely due to adverse reactions. In the VIBERZI treatment groups, the most common reasons for discontinuation due to adverse reactions were constipation (1% for 75 mg and 2% for 100 mg) and abdominal pain (1% for both 75 mg and 100 mg). In comparison, less than 1% of patients in the placebo group withdrew due to constipation or abdominal pain. *Less Common Adverse Reactions* - Adverse reactions that were reported in ≤ 2% of VIBERZI-treated patients are listed below by body system. Gastrointestinal: gastroesophageal reflux disease; General disorders and administration site conditions: feeling drunk; Investigations: increased AST; Nervous system: sedation, somnolence; Psychiatric disorders: euphoric mood; Respiratory: asthma, bronchospasm, respiratory failure, wheezing.

DRUG INTERACTIONS: The metabolism of eluxadoline by CYP pathways has not been clearly established. In addition, the potential of eluxadoline to inhibit CYP3A4 in the gut has not been established. **Tables 2** and **3** include drugs which demonstrated a clinically important drug interaction with VIBERZI or which potentially may result in clinically relevant interactions. **Table 2: Established and Other Potentially Clinically Relevant Interactions Affecting VIBERZI: OATP1B1 Inhibitors -** *Clinical Impact:* Increased exposure to eluxadoline when coadministered with cyclosporine *[see Clinical Pharmacology in full Prescribing Information]. Intervention:* Administer VIBERZI at a dose of 75 mg twice daily *[see Dosage and Administration in full Prescribing Information]* and monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions]*. *Examples:* cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinavir, ritonavir, saquinavir, tipranavir), rifampin, eltrombopag. **Strong CYP Inhibitors* -** *Clinical Impact:* Potential for increased exposure to eluxadoline *[see Clinical Pharmacology in full Prescribing Information]. Intervention:* Monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions]. Examples:* ciprofloxacin, (CYP1A2), gemfibrozil (CYP2C8), fluconazole, (CYP2C19), clarithromycin (CYP3A4), paroxetine and bupropion, (CYP2D6). **Drugs that Cause Constipation -** *Clinical Impact:* Increased risk for constipation related adverse reactions and potential for constipation related serious adverse reactions. *Intervention:* Avoid use with other drugs that may cause constipation (see below); loperamide may be used occasionally for acute management of severe diarrhea but avoid chronic use. Discontinue loperamide immediately if constipation occurs. *Examples:* alosetron, anticholinergics, opioids.*As a precautionary measure due to incomplete information on the metabolism of eluxadoline. **Table 3: Established and Other Potentially Clinically Relevant Interactions Affecting Drugs Co-Administered with VIBERZI: OATP1B1 and BCRP Substrate -** *Clinical Impact:* VIBERZI may increase the exposure of co-administered OATP1B1 and BCRP substrates. Increased exposure to rosuvastatin when co-administered with VIBERZI with a potential for increased risk of myopathy/rhabdomyolysis *[see Clinical Pharmacology in full Prescribing Information]. Intervention:* Use the lowest effective dose of rosuvastatin (see prescribing information of rosuvastatin for additional information on recommended dosing). **CYP3A Substrates with Narrow Therapeutic Index -** *Clinical Impact:* Potential for increased exposure of co-administered drug *[see Clinical Pharmacology in full Prescribing Information]. Intervention:* Monitor drug concentrations or other pharmacodynamic markers of drug effect when concomitant use with eluxadoline is initiated or discontinued. *Examples:* alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus.

USE IN SPECIFIC POPULATIONS: Pregnancy - *Risk Summary:* There are no studies with VIBERZI in pregnant women that inform any drug-associated risks. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies. In animal reproduction studies, oral and subcutaneous administration of eluxadoline to rats and rabbits during organogenesis at doses approximately 51 and 115 times the human exposure after a single oral dose of 100 mg, respectively, demonstrated no teratogenic effects. In a pre- and postnatal development study in rats, no adverse effects were observed in offspring with oral administration of eluxadoline at doses approximately 10 times the human exposure *[see Data]. Data* - Animal Data: Eluxadoline administered as combined oral (1000 mg/kg/day) and subcutaneous (5 mg/kg/day) doses during the period of organogenesis to rats and rabbits (exposures about 51 and 115 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) did not cause any adverse effects on embryofetal development. A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at oral doses of eluxadoline up to 1000 mg/kg/day (with exposures about 10 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). In the same study, eluxadoline was detected in the milk of lactating rats administered oral doses of 100, 300 and 1000 mg/kg/day (with exposures about 1.8, 3 and 10 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). Milk samples were collected from six lactating females per group on lactation day 12. Mean concentrations of eluxadoline in the milk of lactating rats on lactation day 12 were 2.78, 5.49 and 44.02 ng/mL at 100, 300 and 1000 mg/kg/day, respectively. **Lactation -** *Risk Summary:* No data are available regarding the presence of eluxadoline in human milk, the effects of eluxadoline on the breastfed infant, or the effects of eluxadoline on milk production. However, eluxadoline is present in rat milk *[see Use in Specific Populations]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIBERZI and any potential adverse effects on the breastfed infant from VIBERZI or from the underlying maternal condition. **Pediatric Use -** Safety and effectiveness in pediatric patients have not been established. *Juvenile Toxicology Data:* Eluxadoline was orally administered to juvenile rats at 500, 750, and 1500 mg/kg/day (about 16, 54 and 30 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) for 4 weeks. There were no adverse physiologic effects related to eluxadoline. Based on these results, the NOAEL for male and female juvenile rats was 1500 mg/kg/day (about 30 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). **Geriatric Use -** Of 1795 IBS-D patients in clinical trials of VIBERZI who received 75 mg or 100 mg twice daily, 139 (7.7%) were at least 65 years of age, while 15 (0.8%) were at least 75 years old. No overall differences in effectiveness were observed between these patients and younger patients. There were no overall differences in the types of adverse reactions observed between elderly and younger patients; however, a higher proportion of elderly patients than younger patients experienced adverse reactions (66% vs 59%), serious adverse reactions (9% vs 4%), and gastrointestinal adverse reactions (39% vs 28%). **Hepatic Impairment -** Plasma concentrations of eluxadoline increase in patients with hepatic impairment *[see Clinical Pharmacology in full Prescribing Information]*. VIBERZI is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) as plasma concentrations of eluxadoline increase significantly (16-fold) and there is no information to support the safety of VIBERZI in these patients. In patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, plasma concentrations of eluxadoline increase to a lesser extent (6- and 4-fold, respectively). Administer VIBERZI at a reduced dose of 75 mg twice daily to these patients *[see Dosage and Administration in full Prescribing Information]*. Monitor patients with any degree of hepatic impairment for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions]*.

DRUG ABUSE AND DEPENDENCE: Controlled Substance - VIBERZI is listed in Schedule IV of the Controlled Substances Act. **Abuse -** In a drug discrimination study in monkeys, intravenous administration of eluxadoline hydrochloride produced full generalization to the morphine cue. In a self-administration study in monkeys, eluxadoline hydrochloride was self-administered to a degree that was less than that of heroin but greater than that of saline. Adverse reactions of euphoria and feeling drunk were reported in clinical trials of IBS-D evaluating 75 mg and 100 mg doses of VIBERZI. The rate of euphoria was 0% for 75 mg and 0.2% (2/1032) for 100 mg and the rate of feeling drunk was 0.1% (1/807) for 75 mg and 0.1% (1/1032) for 100 mg. In contrast, in two human abuse potential studies conducted in recreational opioid-experienced individuals, supratherapeutic oral doses of VIBERZI (300 mg and/or 1000 mg) and intranasal doses of VIBERZI (100 mg and/or 200 mg) produced the adverse reaction of euphoria (at a rate ranging from 14% to 28%) that was greater than that of placebo (0% to 5%) but less than that of oxycodone (44% to 76%). In the two human abuse potential studies, supratherapeutic oral and intranasal doses of VIBERZI produced small but significant increases in positive subjective measures such as Drug Liking and High compared to placebo. Supratherapeutic oral and intranasal doses of VIBERZI also produced small but significant increases in negative subjective measures such as Drug Disliking and Dysphoria compared to placebo. In the same studies, oxycodone (30 mg and 60 mg oral, and 15 and 30 mg intranasal) produced significantly greater responses on positive and negative subjective measures than those produced by eluxadoline and placebo. **Dependence -** In studies with monkeys and rats in which eluxadoline and eluxadoline hydrochloride were chronically administered, discontinuation of the drug did not lead to behavioral signs of withdrawal, a measure of physical dependence. However, the ability of eluxadoline hydrochloride in monkeys to induce self-administration suggests that the drug is sufficiently rewarding to produce reinforcement. In two human abuse potential studies with VIBERZI conducted in recreational opioid-experienced individuals, euphoria was reported at a rate of 14% to 28%. These data suggest that eluxadoline may produce psychological dependence.

OVERDOSAGE: No reports of overdosage with VIBERZI have been reported. In the event of acute overdose, the stomach should be emptied and adequate hydration maintained. The patient should be carefully observed and given standard supportive treatment as required. Given eluxadoline's action at opioid receptors, administration of a narcotic mu-opioid antagonist, such as naloxone, should be considered. Considering the short half-life of naloxone, repeated administration may be necessary. In the event of naloxone administration, subjects should be monitored closely for the return of overdose symptoms, which may indicate need for repeated naloxone injection.

Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: June 2015 ELX32306 - A - 05/15

Please also see full Prescribing Information at www.VIBERZI.com.

PIPELINE TRENDS

RECENT APPROVALS				
Drug	Manufacturer	Application Type	Approval Date	Indication
Epclusa® (sofosbuvir; velpatasvir)	Gilead	NDA	6/28/2016	Hepatitis C genotype 1
Epclusa (sofosbuvir; velpatasvir)	Gilead	NDA	6/28/2016	Hepatitis C genotype 3
Rayaldee (calcifediol)	OPKO Health, Inc.	505b2 NDA	6/17/2016	Secondary hyperparathyroidism associated with chronic kidney disease
GoNitro® (nitroglycerin)	G. Pohl-Boskamp	NDA	6/8/2016	Angina pectoris due to coronary artery disease
Lansoprazole	Dexcel	505b2 NDA	6/7/2016	Gastroesophageal reflux disease
Byvalson® (nebivolol; valsartan)	Forest Actavis Allergan	NDA	6/3/2016	Hypertension
Netspot® (gallium Ga 68 dotatate)	Advanced Accelerator Applications	NDA	6/1/2016	For scintigraphic localization of neuroendocrine tumors
Teflaro® (ceftaroline fosamil)	Cerexa Allergan Actavis	sNDA	5/27/2016	Acute bacterial skin and skin structure infections (ABSSSI)
Teflaro (ceftaroline fosamil)	Cerexa Allergan Actavis	sNDA	5/27/2016	Community-acquired bacterial pneumonia
Axumin® (fluciclovine [18F])	Blue Earth Diagnostics	NDA	5/27/2016	For diagnostic imaging in prostate cancer
Crestor® (rosuvastatin calcium)	AstraZeneca	sNDA	5/27/2016	Homozygous familial hypercholesterolemia
Zinbryta® (daclizumab)	Biogen AbbVie	BLA	5/27/2016	Relapsing multiple sclerosis
Jentadueto XR® (linagliptin; metformin hydrochloride)	Boehringer Ingelheim Eli Lilly	NDA	5/27/2016	Type 2 diabetes
Ocaliva (obeticholic acid)	Intercept Pharma	NDA	5/27/2016	Primary biliary cholangitis
Afstyla® (coagulation factor VIII recombinant unique single chain)	CSL Behring	BLA	5/26/2016	Hemophilia A
Probuphine® (buprenorphine hydrochloride)	Titan Pharmaceuticals Braeburn Pharmaceuticals	NDA	5/26/2016	Opioid dependence
Doryx MPC® (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Amebiasis
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Anthrax
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Bacterial conjunctivitis
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Bacterial infections caused by certain microorganisms
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Complicated or uncomplicated UTI caused by certain organisms
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Gonorrhea
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Klebsiella granulomatis or Haemophilus ducreyi infections
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Plague
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Prophylaxis of malaria
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Respiratory tract infection
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Rickettsial infections
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Severe acne
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Uncomplicated urethral endocervical or rectal chlamydia infections
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Syphilis
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Nongonococcal urethritis
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Listeriosis
Doryx MPC (doxycycline hyclate)	Mayne Pharma	sNDA	5/20/2016	Chlamydia trachomatis infections
Tecentriq® (atezolizumab)	Roche Genentech	BLA	5/18/2016	Bladder cancer
Opdivo® (nivolumab)	Ono Pharmaceutical Bristol-Myers Squibb	sBLA	5/17/2016	Hodgkin's lymphoma
Lenvima® (lenvatinib mesylate)	Eisai	sNDA	5/13/2016	Metastatic kidney cancer

Ameluz® (aminolevulinic acid hydrochloride)	Biofrontera	NDA	5/10/2016	Actinic keratosis
Otovel® (ciprofloxacin; fluocinolone acetonide)	Laboratorios Salvat	505b2 NDA	4/29/2016	Acute otitis media caused by certain organisms
Nuplazid® (pimavanserin tartrate)	Acadia Pharmaceuticals	NDA	4/29/2016	Psychosis associated with Parkinson's disease
Akovaz® (ephedrine sulfate)	Flamel Technologies	505b2 NDA	4/29/2016	Treatment of hypotension resulting from anesthesia
Fycompa® (perampanel)	Eisai	NDA	4/29/2016	Primary generalized tonic-clonic seizures
Fycompa (perampanel)	Eisai	NDA	4/29/2016	Partial onset seizures in epilepsy
Acticlate Cap® (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Amebiasis
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Anthrax
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Bacterial conjunctivitis
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Bacterial infections caused by certain microorganisms
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Complicated or uncomplicated UTI caused by certain organisms
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Gonorrhea
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	*Klebsiella granulomatis* or *Haemophilus ducreyi* infections
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Plague
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Prophylaxis of malaria
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Rickettsial infections
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Severe acne
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Uncomplicated urethral endocervical or rectal chlamydia infections
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Syphilis
Acticlate Cap (doxycycline hyclate)	Aqua Pharmaceuticals Almirall	505b2 NDA	4/26/2016	Listeriosis

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RECENT APPROVALS *continued from page 53*

Xtampza ER® (oxycodone)	Collegium	505b2 NDA	4/26/2016	Chronic pain
Cabometyx® (cabozantinib S-Malate)	Exelixis	505b2 NDA	4/25/2016	Kidney cancer
Bevespi Aerosphere® (glycopyrrolate; formoterol fumarate)	AstraZeneca; Pearl Therapeutics	505b2 NDA	4/25/2016	Moderate to severe COPD
Orfadin® (nitisinone)	Rare Disease Therapeutics; Swedish Orphan Biovitrum	NDA	4/22/2016	Hereditary tyrosinemia type 1
Photrexa Viscous® (riboflavin 5-phosphate; dextran)	Avedro	NDA	4/15/2016	Keratoconus
Venclexta® (venetoclax)	AbbVie; Roche Genentech	NDA	4/11/2016	Chronic lymphocytic leukemia
BromSite® (bromfenac)	InSite Vision, Inc.	505b2 NDA	4/11/2016	Postoperative pain
ProvayBlue® (methylene blue)	Provepharm	505b2 NDA	4/8/2016	Methemoglobinemia
Inflectra® (infliximab-dyyb)	Celltrion Pfizer Hospira	Biosimilar	4/5/2016	Ankylosing spondylitis
Inflectra (infliximab-dyyb)	Celltrion Pfizer Hospira	Biosimilar	4/5/2016	Crohn's disease
Inflectra (infliximab-dyyb)	Celltrion Pfizer Hospira	Biosimilar	4/5/2016	Plaque psoriasis
Inflectra (infliximab-dyyb)	Celltrion Pfizer Hospira	Biosimilar	4/5/2016	Psoriatic arthritis
Inflectra (infliximab-dyyb)	Celltrion Pfizer Hospira	Biosimilar	4/5/2016	Rheumatoid arthritis
Inflectra (infliximab-dyyb)	Celltrion Pfizer Hospira	Biosimilar	4/5/2016	Ulcerative colitis
Descovy® (emtricitabine; tenofovir alafenamide fumarate)	Gilead	NDA	4/4/2016	HIV infection

PRODUCT PIPELINE

Drug	Manufacturer	PDUFA Date	Application Type	Expected Indication
Andexanet alfa	Portola Pharmaceuticals	8/17/2016	BLA	Reverse anticoagulant activity of direct and indirect Factor Xa inhibitors
Etelcalcetide (AMG 416)	Amgen	8/24/2016	NDA	Treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis
Orkambi® (lumacaftor; ivacaftor)	Vertex Pharmaceuticals	9/30/2016	sNDA	Cystic fibrosis patients with two copies of F508del mutation
ABP-501® (adalimumab)	Amgen	9/25/2016	Biosimilar	Psoriatic arthritis; rheumatoid arthritis; juvenile idiopathic arthritis; ulcerative colitis; ankylosing spondylitis; plaque psoriasis; pediatric Crohn's disease; Crohn's disease
Remoxy® (oxycodone)	Durect Pain Therapeutics	9/25/2016	505b2 NDA	Chronic pain
Yosprala® (aspirin; omeprazole)	Aralez	9/14/2016	NDA	Prevention of cardiovascular disease
Xeglyze® (abametapir)	Hatchtech Dr. Reddy's	9/2016	NDA	Head lice infection
Blincyto® (blinatumomab)	Amgen Onyx	9/01/2016	sBLA	Pediatric Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia; acute lymphoblastic leukemia; non-Hodgkin's lymphoma
Parsabiv® (velcalcetide)	Amgen	8/24/2016	NDA	Secondary hyperparathyroidism associated with chronic kidney disease
Keytruda® (pembrolizumab)	Merck & Co.	8/9/2016	sBLA	Metastatic head and neck cancer; urothelial cancer; gastric cancer; colorectal cancer; triple negative breast cancer; esophageal cancer; gastroesophageal junction cancer; multiple myeloma; Hodgkin's lymphoma; liver cancer; tumors; kidney cancer
LixiLan® (insulin glargine + Lixisenatide)	Sanofi	8/2016	NDA	Type 2 diabetes
Zinplava® (bezlotoxumab)	Merck &Co.	7/23/2016	BLA	Prevention of *Clostridium difficile* infection (CDI) recurrence
Lifitegrast	Shire	7/22/2016	NDA	Dry eye

Vesneo® (latanoprostene bunod)	Bausch & Lomb NicOx	7/21/2016	NDA	Glaucoma ocular hypertension
Relistor® (methylnaltrexone bromide)	Salix Progenics	7/19/2016	NDA	Constipation
LA-EP2006® (pegfilgrastim)	Sandoz	7/2016	Biosimilar	Cancer patients receiving myelosuppressive chemotherapy
Lyxumia® (lixisenatide)	Sanofi Zealand Pharma	7/2016	NDA	Type 2 diabetes
Syndros® (dronabinol)	Insys Therapeutics	7/1/2016	NDA	Chemotherapy-induced nausea and vomiting (CINV); cachexia or an unexplained significant weight loss in AIDS
Aggrastat® (tirofiban hydrochloride)	Medicure Inc.	7/10/16	NDA	ST segment elevation myocardial infarction (STEMI) intended for percutaneous coronary intervention
SequestOX® (naltrexone; oxycodone hydrochloride)	Elite Pharmaceuticals, Inc.	7/14/16	NDA	Management of moderate to severe pain where the use of opioid analgesic is appropriate
RI-002	Adma Biologics, Inc.	7/21/16	BLA	Primary immunodeficiency population
Dextenza® (dexamethasone)	Ocular Therapeutix, Inc.	7/24/16	NDA	Ocular pain following ophthalmic surgery
Arzerra® (ofatumumab)	Genmab	9/10/16	sBLA	Relapsed chronic lymphocytic leukemia
Atezolizumab	Roche Holding AG	9/12/16	BLA	Advanced bladder cancer
Yosprala® (aspirin; omeprazole)	Aralez Pharmaceuticals	9/14/16	NDA	Secondary prevention of advanced bladder cancer
Heplisav-B	Dynavax Technologies Corp.	9/15/16	BLA	Immunization against hepatitis B infection in adults over 18 years old

PROJECTED UPCOMING LOEs (THROUGH 4Q16)			
Drug	Brand Manufacturer	Projected LOE Date	Day 1 Entrants
Asacol HD® 800 mg (mesalamine)	Warner Chilcott; Actavis; Allergan	7/01/2016	1
Zegerid® 20/1680 (powder for oral suspension) (omeprazole; sodium bicarbonate)	Santarus; Salix; Valeant	7/15/2016	1
Zegerid 40/1680 (powder for oral suspension) (omeprazole; sodium bicarbonate)	Santarus; Salix; Valeant	7/15/2016	1
Zegerid OTC (powder for oral suspension) (omeprazole; sodium bicarbonate)	MSD Consumer Products Inc.; Santarus; Merck & Co.	7/15/2016	TBD
Prolensa® (bromfenac sodium)	Bausch & Lomb; Valeant	7/25/2016	1
Ziana® (clindamycin phosphate; tretinoin)	Medicis; Valeant	7/2016	1
Aczone® 5% (dapsone)	Allergan	9/11/2016	TBD
Zirgan® (ganciclovir)	Bausch & Lomb; Valeant	9/15/2016	TBD
Retin-A Micro® 0.08% (tretinoin)	Valeant	9/21/2016	TBD
Aciphex® Sprinkle capsules (rabeprazole sodium)	Eisai; FSC Laboratories; Flamel Technologies	9/26/2016	TBD
Beyaz® (drospirenone; ethinyl estradiol; levomefolate calcium)	Bayer	3Q2016	1
Safyral® (drospirenone; ethinyl estradiol; levomefolate calcium)	Bayer	3Q2016	1

RESOURCES

1. **www.drugs.com/newdrugs.html**
2. **www.fdatracker.com/fda-calendar/**
3. **www.rttnews.com/corpinfo/fdacalendar.aspx**
4. **www.ipdanalytics.com/**
5. **www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/FA25AE/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/56A3BE/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=1034&contentSetId=50&title=INVESTIGATIONAL+DRUGS+-+NEW+DRUG+APPLICATION+%28NDA%29+STATUS&servicesTitle=INVESTIGATIONAL+DRUGS+-+NEW+DRUG+APPLICATION+%28NDA%29+STATUS**
6. **https://amcp.edossiers.com/module/module_generic.aspx?ModuleID=4006&CTRL=ListUpdates&DrugupdateTypeID=50**

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