

PI3K Inhibitors:  
Pipeline and  
Therapeutic Advances

Multiple Myeloma:  
Future Directions in  
Treatment

PARP Inhibitors in Ovarian  
Cancer: Management  
Considerations

Opioid Use Disorder:  
Managed Care  
Implications

# Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Fall 2018

**Multiple  
Sclerosis:**  
Current and Pipeline  
Treatments and Their Impact

**MagellanRx**  
MANAGEMENT<sup>SM</sup>  
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# Welcome to the Magellan Rx Report

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**Mostafa Kamal**  
Chief Executive Officer  
Magellan Rx Management

## Dear Managed Care Colleagues,

Welcome to our fall issue of the Magellan Rx™ Report! It's been another exciting year for managed care pharmacy, with several new drug approvals since the summer issue. Once again, Magellan Rx Management was poised to prepare payers

for these approvals with the quarterly MRx Pipeline, which offers clinical insights and marketplace intelligence on anticipated specialty and traditional drugs in the pipeline.

In this issue of the Magellan Rx™ Report, the multiple sclerosis cover story reviews the current treatment landscape and highlights the numerous pipeline agents in development.

A second article of focus explores the current treatment landscape for multiple myeloma, discussing future directions for treatment with the use of novel immunotherapeutic approaches, including use of novel monoclonal antibodies, vaccines, adoptive T-cell therapies, and chimeric antigen receptor therapies, and the impact on managed care.

Another article of interest discusses opioid use disorder and the various treatment options available, with an emphasis on treating the symptoms associated with opioid withdrawal and information regarding an investigational therapy in development.

Other notable topics featured in this issue include a budget impact model for PARP inhibition; advancements in the treatment of cancer through PI3K inhibition; and key

findings from a payer panel discussion regarding toxin management for therapeutic use.

No issue of the Report would be complete without a pharmaceutical pipeline review to help you track promising new agents that may receive FDA approval in the near future. To learn more about Magellan Rx Management and our support of payer initiatives of the future, please feel free to contact us at [MagellanRxReport@magellanhealth.com](mailto:MagellanRxReport@magellanhealth.com). As always, I value any feedback that you may have, and thanks for reading!

Sincerely,

**Mostafa Kamal**  
Chief Executive Officer  
Magellan Rx Management

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# Managed Care Newsstand

## FDA Revises Clinical Endpoints for Demonstrating Effectiveness of New MAT Drugs

Claire Wulf Winiarek

On August 6, the U.S. Food and Drug Administration (FDA) released draft industry guidance revising clinical endpoints for drugmakers to demonstrate the effectiveness of new medication-assisted treatment (MAT) therapies for opioid use disorder (OUD).<sup>1</sup> Traditionally, MAT drugs' effectiveness or success has been measured based on whether a patient in recovery stopped using opioids. The new guidance proposes giving greater weight to reductions in relapse overdoses, infectious disease transmission, and "adverse outcomes of OUD" (e.g., mortality). It also pro-

poses measuring effectiveness using a patient-reported outcome survey, with such primary endpoints as "change in drug use patterns" and such secondary endpoints as "intensity of the urge" or improvements in sleep or mood.

FDA Commissioner Scott Gottlieb tweeted the draft guidance is a step "to

encourage more widespread innovation and development of MAT drugs," though it is unclear if the proposal will encourage new MAT therapies more effective than current therapies.

<sup>1</sup>FDA. Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment. August 2018.

*"Traditionally, MAT drugs' effectiveness or success has been measured based on whether a patient in recovery stopped using opioids. The new guidance proposes giving greater weight to reductions in relapse overdoses, infectious disease transmission, and 'adverse outcomes of OUD' (e.g., mortality)."*

## CMS Announces MA Plans May Use Step Therapy for Part B Drugs in 2019

Reflecting concepts included in the Trump Administration's May 2018 Blueprint to Lower Drugs Prices and Reduce Out-of-Pocket Costs, the Centers for Medicare & Medicaid Services (CMS)

released a Health Plan Management System memo to Medicare Advantage (MA) organizations allowing MA plans to use step therapy edits for Medicare Part B drugs as part of their drug management care coordination services beginning January 1, 2019. The August 7 memo also rescinded the agency's September 17, 2012, memo, which pro-

hibited the use of step therapy.

The memo laid out several limitations, qualifiers, and related requirements for care coordination activities, including that patients currently in therapy are grandfathered in and step therapy should not increase beneficiary costs.

## CMS Issues Medicare Part B Step Therapy FAQs

Claire Wulf Winiarek

On August 29, CMS posted on its website a document providing answers to several questions posed by stakeholders, including Magellan Health, on the

use of step therapy for Medicare Part B drugs in the coming benefit year (2019). Of note, CMS states Part B step therapy limits need not be reported to CMS (Page 3) and plans are permitted to make mid-year changes to step therapy if consistent with the plan's Annual Notice of Change and Evidence of Coverage (Page 4).

While CMS believes it has answered all step-therapy related questions, Government Affairs and its industry trade group, PCMA, have identified instances of partial answers and will be following up with CMS to better address these.

## Indication-Based Pricing and Billing Challenges

*MRx Trend Alert | August 2018 | Volume 5, Issue 3*

The FDA approved two chimeric anti-gen receptor (CAR-T) cell therapies in 2017. Tisagenlecleucel (Kymriah) was approved on August 30, 2017, for the treatment of relapsed/refractory B-cell acute lymphoblastic leukemia in patients up to 25 years. On May 1 of this year, the FDA approved Kymriah for a second indication of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) in adult patients. Meanwhile, Gilead's axicabtagene ciloleucel (Yescarta) was approved for DLBCL on October 18, 2017.

CMS assigned a temporary Q-code of Q2040 for Kymriah, effective January 1, which will be used for both Kymriah indications. Novartis has assigned two different National Drug Codes (NDCs) for Kymriah to address the different indications. Both agents also have a handful of other potential indications in the pipeline.

Health plans will need to pay close

*"If a health plan is only accepting the assigned temporary Q-code, the claim could be reimbursed at the wrong rate, causing a potential over- or underpayment. Most health plans are currently adjudicating CAR-T medical claims on a case-by-case basis due to the high cost, so chances of the wrong payment being reimbursed are lessened."*

attention to how medical claims for Kymriah will be reimbursed based on patient diagnosis. Some health plans do not accept/receive NDC numbers on the medical claims for medications when billed through the medical benefit. If a health plan is only accepting the assigned temporary Q-code, the claim could be reimbursed at the wrong rate, causing a potential over- or underpay-

ment. Most health plans are currently adjudicating CAR-T medical claims on a case-by-case basis due to the high cost, so chances of the wrong payment being reimbursed are lessened. As these treatments become more common and additional indications are approved, health plans will need to ensure they have automated NDC-level claim information to reimburse for Kymriah.

## Annual Leading Human to Healthy, Vibrant Lives Conference

In September, Magellan's Government Affairs team, in partnership with Capital BlueCross, hosted a conference exploring solutions to the opioid epidemic. Magellan Healthcare Chief Medical Officer for Behavioral Health and Specialty Caroline Carney, Capital

BlueCross Chief Medical Officer Jennifer Chambers, and National Institute on Drug Abuse Director Carlos Blanco addressed the conference as keynote speakers, and former Substance Abuse and Mental Health Services Administration Administrator Charley Curie led a plenary session. Attendees also heard from Pennsylvania Department of Human Services Secretary Teresa D. Miller,

who made a call for action:

"As I meet with healthcare providers, stakeholders, and people my department serves, I often hear that healthcare exists in silos. ... We cannot just treat a substance use disorder, mental health concern, or physical health need on their own – in many cases, they are interconnected or treatment of one can affect how to best treat another."



*It Began*

## INDICATIONS

### **Adult Ulcerative Colitis (UC)**

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

### **Adult Crohn's Disease (CD)**

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

## IMPORTANT SAFETY INFORMATION

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

## In UC & CD

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

With...

 **Entyvio**<sup>®</sup>  
vedolizumab

### Long-term focus—from the start:

#### GI-FOCUSED ACTION

Entyvio specifically binds to  $\alpha 4\beta 7$  integrin, blocking its interaction with MAdCAM-1, which is mainly expressed on gut endothelial cells<sup>1</sup>

#### WITH

#### REMISSION ACHIEVED

UC and CD patients achieved remission at 52 weeks vs placebo. Studies included bio-naïve and anti-TNF $\alpha$ -experienced patients<sup>1,2</sup>

#### AND

#### 5-YEAR INTEGRATED SAFETY

A 5-year analysis, including an open-label continuation study, demonstrated consistent results with clinical trials across safety parameters<sup>1,3</sup>

Individual results may vary.

*Begin the Change*

### IMPORTANT SAFETY INFORMATION (continued)

- Although no cases of PML have been observed in ENTYVIO clinical trials, JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.

- Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.
- Most common adverse reactions (incidence  $\geq 3\%$  and  $\geq 1\%$  higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

**Please see brief summary of Prescribing Information on adjacent pages.**

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

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## BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

### ENTYVIO (vedolizumab) for injection, for intravenous use

#### INDICATIONS AND USAGE

##### Adult Ulcerative Colitis

ENTYVIO (vedolizumab) is indicated for:

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

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

##### Adult Crohn's Disease

ENTYVIO (vedolizumab) is indicated for:

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

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

#### CONTRAINDICATIONS

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

#### WARNINGS AND PRECAUTIONS

##### Infusion-Related Reactions and Hypersensitivity Reactions

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

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

##### Infections

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

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

##### Progressive Multifocal Leukoencephalopathy

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

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

Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are

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

##### Liver Injury

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

##### Live and Oral Vaccines

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

#### ADVERSE REACTIONS

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

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

##### Clinical Trials Experience

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

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

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

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

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

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

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

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

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

<sup>†</sup>Patients who received ENTYVIO for up to 52 weeks.

<sup>‡</sup>Patients who received placebo for up to 52 weeks.

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

#### Infusion-Related Reactions and Hypersensitivity Reactions

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

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

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

#### Infections

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

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

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

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

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

#### Liver Injury

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

#### Malignancies

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

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

#### Live and Oral Vaccines

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

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

#### Immunogenicity

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

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

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

## **DRUG INTERACTIONS**

### **Natalizumab**

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

### **TNF Blockers**

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

### **Live Vaccines**

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

## **USE IN SPECIFIC POPULATIONS**

### **Pregnancy**

#### Pregnancy Exposure Registry

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

#### Pregnancy Category B:

#### Risk Summary

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

#### Clinical Considerations

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

#### Animal Data

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

### **Nursing Mothers**

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

### **Pediatric Use**

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

### **Geriatric Use**

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

Manufactured by:

**Takeda Pharmaceuticals America, Inc.**

Deerfield, IL 60015

U.S. License No. 1898

For more information, go to [www.ENTYVIO.com](http://www.ENTYVIO.com) or call 1-877-825-3327

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# Opioid Use Disorder:

## Managed Care Implications

According to the 2016 National Survey on Drug Use and Health, an estimated 1.8 million individuals in the U.S. have an opioid use disorder (OUD) related to opioid pain medications, while an additional 626,000 have an OUD related to heroin.<sup>1</sup> Of the 63,600 drug overdose-related deaths that occurred nationwide in 2016, approximately 66% were related to opioids – five times the number seen in 1999.<sup>1</sup> According to the U.S. Centers for Disease Control and Prevention, 115 individuals die from an opioid overdose each day in the U.S.<sup>2</sup> Given the scope and magnitude of this crisis, the U.S. Department of Health & Human Services declared a public health emergency in 2017 to address the opioid crisis.<sup>3</sup>



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Chief Medical Officer  
Magellan Rx Management

In addition to the risk of overdose and death, opioid use can increase exposure to human immunodeficiency virus (HIV), hepatitis, and other infectious conditions that can be transmitted through sharing injection paraphernalia or engaging in other high-risk behaviors as a result of being under the influence of opioids.<sup>4</sup> Furthermore, addiction and overdose have been associated with increased utilization of healthcare services. It has been estimated that the total cost of the opioid epidemic within the U.S. during 2015 was \$504 billion.<sup>5</sup>

### Defining Opioid Use Disorder

The Diagnostic and Statistical Manual

of Mental Disorders, 5th edition (DSM-V) considers OUD a chronic, relapsing condition defined as a “problematic pattern of opioid use that leads to clinically significant impairment or distress” (Table 1).<sup>6</sup> A diagnosis using the older, stricter criteria outlined in DSM-IV is best mapped to patients diagnosed with moderate to severe OUD using the updated DSM-V criteria.<sup>5</sup> As a result, not all patients diagnosed using the criteria in DSM-V will necessarily require treatment.

### Treating OUD

The treatment for OUD ranges from the short-term management of withdrawal to long-term maintenance treatment with a goal of achieving abstinence from the misuse of opioids and prevention of relapse while ensuring the patient’s medical and mental health needs are met.<sup>5</sup>

### Treating Opioid Withdrawal

Withdrawal may begin as soon as eight hours following the last dose of short-acting opioids or up to 36 hours after the last dose of long-acting opioids, and it may last between one to four weeks, depending on the use of short- or long-acting opioid products.<sup>5</sup> Formerly known as detoxification (or detox), medically supervised withdrawal allows for the safe discontinuation of opioids while managing the associated symptoms. In addition to opioid craving, withdrawal symptoms may include flu-like symptoms (e.g., fever, sweating, nausea, vomiting, abdominal cramps, diarrhea, arthralgia, myalgia),

*According to the U.S. Centers for Disease Control and Prevention, 115 individuals die from an opioid overdose each day in the U.S.*

**TABLE 1. OUD DIAGNOSTIC CRITERIA<sup>6</sup>**

A DIAGNOSIS OF OUD REQUIRES PATIENTS EXHIBIT AT LEAST 2 OF THE FOLLOWING SYMPTOMS IN A 12-MONTH PERIOD:

1	Taking opioids in larger amounts or over a longer period of time than intended
2	Having a persistent desire or unsuccessful attempt to reduce or control opioid use
3	Spending excess time obtaining, using, or recovering from opioids
4	Craving for opioids
5	Continuing opioid use causing inability to fulfill work, home, or school responsibilities
6	Continuing opioid use despite having persistent social or interpersonal problems
7	Lack of involvement in social, occupational, or recreational activities
8	Using opioids in physically hazardous situations
9	Continuing opioid use in spite of awareness of persistent physical or psychological problems
10	Tolerance, including need for increased amounts of opioids or diminished effect with continued use at the same amount — as long as the patient is not taking opioids under medical supervision
11	Withdrawal manifested by characteristic opioid withdrawal symptoms or taking opioids to relieve or avoid withdrawal symptoms — as long as the patient is not taking opioids under medical supervision

OUD IS FURTHER CLASSIFIED AS MILD (PRESENCE OF 2-3 SYMPTOMS LISTED ABOVE), MODERATE (PRESENCE OF 4-5 SYMPTOMS LISTED ABOVE), OR SEVERE (PRESENCE OF 6 OR MORE SYMPTOMS LISTED ABOVE) WITHIN A 12-MONTH PERIOD

tachycardia, hypertension, depression, anxiety, and irritability. Symptoms may be severe and may adversely affect a patient’s ability to abstain from opioid use when not properly managed.<sup>5</sup>

Medically supervised withdrawal may be achieved through the use of an opioid agonist (such as methadone or buprenorphine) or an alpha-2 adrenergic agonist (such as clonidine or lofexidine) to help reduce the signs and symptoms associated with opioid withdrawal.<sup>5</sup> Although not U.S. Food and Drug Administration (FDA)-approved for this purpose, clonidine may be used to manage symptoms such as anxiety and irritability and is a recommended feature of withdrawal management according to the American Society

**TABLE 2. TREATMENT OPTIONS FOR OPIOID WITHDRAWAL SYMPTOMS<sup>4,5</sup>**

Symptom	Treatment Options
Anxiety	Benzodiazepines
Diarrhea	Loperamide
Insomnia	Diphenhydramine Trazodone
Nausea	Metoclopramide Ondansetron
Pain (arthralgia, myalgia)	Acetaminophen Nonsteroidal anti-inflammatory drugs (NSAIDs)

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*In addition to opioid craving, withdrawal symptoms may include flu-like symptoms (e.g., fever, sweating, nausea, vomiting, abdominal cramps, diarrhea, arthralgia, myalgia), tachycardia, hypertension, depression, anxiety, and irritability. Symptoms may be severe and may adversely affect a patient's ability to abstain from opioid use when not properly managed.*

of Addiction Medicine.<sup>4</sup> In May 2018, Lucemyra (lofexidine) became the first opioid withdrawal treatment option to gain FDA approval specifically for this purpose.<sup>7,8</sup> Additional treatment options for the various symptoms of opioid withdrawal are summarized in Table 2. While an important part of treatment, addressing the symptoms associated with withdrawal is insufficient unless such treatment is prepared in conjunction with a comprehensive and long-term plan for OUD management.<sup>4,5</sup> Providers should weigh both the costs and benefits associated with each treatment when considering which to use.

### **Maintenance Treatment**

In addition to playing a role in withdrawal management, medication-assisted treatment (MAT) is an important option for the maintenance treatment of OUD.<sup>5</sup> The Substance Abuse and Mental Health Services Administration (SAMHSA) defines MAT as "the use of medications, in combination with counseling and behavioral therapies, to provide a 'whole-patient' approach to the treatment of substance use disorders."<sup>5,9,10</sup> Any treatment plan for OUD should include strategies to prevent relapse and continuously monitor the patient's

opioid use status and the overall management of their use disorder.<sup>4</sup> Opioid treatment programs (OTPs) are specialized programs that are required to obtain accreditation and certification through SAMHSA. These programs are legally required to provide patients with a range of evaluation and treatment services beyond just MAT, including counseling.<sup>9</sup>

Currently, three pharmacological options serve as the mainstay for MAT: the opioid agonists, methadone and buprenorphine; and the opioid antagonist, naltrexone. Each of these three agents exhibits action at mu-opioid receptors to help reduce cravings,

prevent withdrawal symptoms, and normalize functioning without producing the euphoric or harmful effects of the opioid of abuse.<sup>4,5,9</sup> Given the lack of head-to-head trials evaluating the relative efficacy of the various MAT options for OUD, the individual product characteristics can be evaluated to determine what might be the best fit for each patient (Table 3).<sup>5</sup> Additional agents still in development for the treatment of OUD are summarized in Table 4.

It is important that any treatment plan be created in partnership with the patient to ensure individual goals and needs are properly met as there is no one-size-fits-all approach for OUD. When determining the product to use for MAT, consideration should be given to what the patient hopes to get out of treatment, what treatment setting might best suit this patient's lifestyle and living situation, any past experiences the patient may have had with MAT, any comorbid mental or medical disorders, pregnancy status, and use of other substances.<sup>4,5</sup>

The duration of therapy may vary from patient to patient; some may be able to stop using opioids without MAT, some may simply need MAT to manage acute withdrawal, and some may require lifelong MAT to sustain recovery.<sup>5</sup> As with ensuring the specific treatment plan is specific to individual patient goals and needs, it is equally important that the duration of therapy best suits each patient.<sup>5</sup>

*It is important that any treatment plan be created in partnership with the patient to ensure individual goals and needs are properly met as there is no one-size-fits-all approach for OUD.*

**TABLE 3. OUD TREATMENT COMPARISON**<sup>5,11-18</sup>

Agent Name	Methadone	Buprenorphine	Buprenorphine and Naloxone	Naltrexone							
Mu-opioid Receptor Activity	<ul style="list-style-type: none"> <li>Full agonist</li> </ul>	<ul style="list-style-type: none"> <li>Partial agonist</li> </ul>	<ul style="list-style-type: none"> <li>Buprenorphine — partial agonist</li> <li>naloxone — antagonist (naloxone not absorbed sublingually)</li> </ul>	<ul style="list-style-type: none"> <li>Antagonist</li> </ul>							
OID-related Indications	<ul style="list-style-type: none"> <li>Medically supervised withdrawal</li> <li>Maintenance treatment of OUD</li> </ul>	<ul style="list-style-type: none"> <li>SL: Treatment of opioid dependence</li> <li>Intradermal implants: Maintenance treatment of opioid dependence in patients stable on daily dose equivalent to &lt; 8 mg Suboxone or Subutex (or generic equivalent)</li> <li>ER SC injection: Treatment of moderate to severe OUD in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days</li> </ul>	<ul style="list-style-type: none"> <li>Treatment of opioid dependence</li> </ul>	<ul style="list-style-type: none"> <li>Oral: blockade of the effects of exogenously administered opioids</li> <li>ER IM: prevents relapse to opioid dependence, following medically supervised opioid withdrawal</li> </ul>							
Available Dosage Forms	<b>GENERIC FORMULATIONS</b>		<b>GENERIC FORMULATIONS*</b>		<b>GENERIC FORMULATIONS</b>		<b>GENERIC FORMULATIONS</b>				
	<ul style="list-style-type: none"> <li>Injection</li> <li>Oral concentrate</li> <li>Oral solution</li> <li>Oral tablet</li> <li>Tablet for oral suspension</li> </ul>		<ul style="list-style-type: none"> <li>SL tablet<sup>b</sup></li> </ul>		<ul style="list-style-type: none"> <li>SL tablets</li> <li>SL film</li> </ul>		<ul style="list-style-type: none"> <li>Oral tablet</li> </ul>				
	Product Name	Route of Administration	Product Name	Route of Administration	Frequency	Product Name	Route of Administration	Frequency	Product Name	Route of Administration	Frequency
	Dolophine	Oral tablet	Probuphine	Intradermal implant	Implants last up to 6 months	Bunavail	Buccal film	Daily	Revia	Oral tablet (discontinued)	Daily, every other day, three times per week
	Methadose	Oral concentrate				Sublocade	ER SC injection	Monthly			
	Methadose	Oral tablet				Zubsolv	SL tablet	Daily	Vivitrol	ER IM injection)	Monthly
	Methadose	Tablet for oral suspension									
Dosing Considerations	<ul style="list-style-type: none"> <li>Pharmacokinetics vary across individuals; average T<sub>1/2</sub>=24 hours (range 8-59 hours).</li> <li>There is no ceiling effect and steady state is achieved in ~5 days. Important to start doses low and increases slowly</li> </ul>	<ul style="list-style-type: none"> <li>Pharmacokinetics vary greatly across individuals; average T<sub>1/2</sub>=24-42 hours.</li> <li>Due to high affinity for the mu-opioid receptor, buprenorphine may displace other opioids if dosing is not properly timed with the last dose of opioid taken.</li> <li>Initiation should occur at least 6-12 hours after the last use of short-acting opioids or 24-72 hours after the last use of long-acting opioids.</li> <li>Consideration should be given to observing induction therapy in provider's office. Buprenorphine exhibits a ceiling effect at mu-opioid receptors.</li> </ul>	<ul style="list-style-type: none"> <li>Due to antagonist activity at mu-opioid receptors, important to ensure patient has been opioid-free for 7-10 days (confirmed by urinalysis) before initiating naltrexone to minimize risk of precipitated opioid withdrawal.</li> </ul>								
Schedule and Access	<p>Schedule II</p> <ul style="list-style-type: none"> <li>When used for the treatment of OUD, methadone may only be dispensed through federally certified OTPs in accordance with the guidelines provided by the SAMHSA Center for Substance Abuse Treatment. (Individual state regulations may vary).</li> <li>Exceptions are permitted:                             <ol style="list-style-type: none"> <li>To allow continuation of an established methadone dose when a patient may be hospitalized for a reason other than OUD and</li> <li>For an emergency period of up to 3 days while proper addiction treatment can be secured in an appropriate facility</li> </ol> </li> </ul>	<p>Schedule III</p> <ul style="list-style-type: none"> <li>SL buprenorphine-containing products may be obtained in an outpatient setting for in-home, unsupervised dosing when prescribed by authorized providers. Such authorized prescribers are then subject to certain limitations on the number of patients they can be treating at a given time.</li> <li>In addition to prescribing restrictions for SL buprenorphine:                             <ol style="list-style-type: none"> <li>The distribution of the ER SC formulation is subject to further restrictions outlined in the Sublocade REMS program requiring pharmacies and the healthcare settings in which they dispense receive special certification. This formulation cannot be dispensed directly to patients.</li> <li>Prescribing and insertion of the intradermal implant is limited to providers who have completed specialized live training and certification under the Probuphine REMS program.</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>Not a federally scheduled medication</li> <li>Naltrexone can be prescribed by any healthcare provider with prescribing capabilities.</li> </ul>								

**TABLE 3. OUD TREATMENT COMPARISON<sup>5,11-18</sup>(CONT.)**

Agent Name	Methadone	Buprenorphine	Buprenorphine and Naloxone	Naltrexone
Advantages	<ul style="list-style-type: none"> <li>• Can be used for withdrawal and maintenance treatment</li> <li>• Long half-life and duration of action</li> <li>• Administration in OTPs ensures daily interactions with healthcare provider, may provide greater access to medical and supportive psychosocial interventions, and minimizes the risk of diversion and misuse</li> <li>• Preferred treatment option in pregnancy</li> <li>• Generically available</li> </ul>	<ul style="list-style-type: none"> <li>• Can be used for withdrawal and maintenance treatment</li> <li>• May result in less sedation than methadone and has a lower risk of respiratory depression, due to ceiling effect of opioid actions</li> <li>• Fewer clinically relevant drug interactions than methadone</li> <li>• SL tablets allow for discreet, at-home dosing and may provide patients with a ritual that helps them feel in control of their recovery</li> <li>• Single-entity products are an alternative treatment option to methadone during pregnancy</li> <li>• Coformulation with naloxone helps deter some methods of misuse</li> <li>• Lower risk of diversion with intradermal implants with ER SC formulation</li> <li>• Many formulations are generically available</li> </ul>	<ul style="list-style-type: none"> <li>• Provides patients with a non-opioid treatment option with no abuse liability and no risk of diversion</li> <li>• Not bound by specific regulatory restrictions</li> <li>• Does not cause withdrawal when treatment is stopped</li> <li>• No risk of sedation or respiratory depression</li> </ul>	
Disadvantages	<ul style="list-style-type: none"> <li>• Daily requirement to travel to treatment facility may not suit the lifestyle of all patients. (However, at-home dosing may be allowed under certain circumstances)</li> <li>• May not be suitable for all patients given potential for QTc prolongation</li> <li>• Because this agent is a full agonist, risk of lethal overdose is greater than with buprenorphine</li> <li>• Patients need to meet criteria for treatment in an OTP</li> <li>• May result in withdrawal symptoms if treatment is stopped abruptly</li> <li>• Risk of overdose with concomitant alcohol or benzodiazepine use</li> </ul>	<ul style="list-style-type: none"> <li>• If initial dosing is not timed properly with opioid cessation, withdrawal may be precipitated</li> <li>• Authorized prescribers are limited in the number of patients they can see, which may limit access to treatment</li> <li>• Certain dosage forms require in-office administration vs. convenient at-home dosing</li> <li>• Unsupervised dosing may increase risk of nonadherence, diversion, or misuse</li> <li>• Proper treatment cessation requires slow tapering over several months</li> <li>• Risk of overdose with concomitant alcohol or benzodiazepine use. Coformulation with naloxone can't be used during pregnancy. Not all strengths of SL tablets and films are interchangeable; exposure to active ingredients may vary across formulations</li> </ul>	<ul style="list-style-type: none"> <li>• Mu-opioid receptor blockade may be overridden with high doses of opioids</li> <li>• May precipitate withdrawal if patient is not sufficiently opioid-free upon initiation</li> <li>• Cannot mitigate withdrawal symptoms or control cravings due to lack of opioid activity</li> <li>• Low rate of patient acceptance; non-adherence rates are high with oral formulation</li> <li>• Contraindicated in patients with severe hepatic impairment</li> <li>• Cannot be used during pregnancy</li> <li>• May complicate ability to achieve adequate pain control if an acute indication presents itself (e.g., injury, surgery)</li> </ul>	

<sup>a</sup>Single-ingredient buprenorphine products intended for pain management are excluded from this table

<sup>b</sup>Subutex (buprenorphine) SL tablets have been discontinued

<sup>c</sup>Generic equivalent still available

Abbreviations: ER: extended release, IM: intramuscular, IR: immediate release, OUD: opioid use disorder, OTP: opioid treatment program, REMS: risk evaluation and mitigation strategies, SC: subcutaneous, SL: sublingual

### Implications for Managed Care

When considering formulary placement and drug policies related to the various agents used to treat OUD (including those for opioid withdrawal and overdose), it is important to consider the scale of the public health crisis associated with this condition. Given that treatment selection and duration are patient-specific, any limits on accessing individual agents or to duration of therapy should be adopted with caution as they may result in barriers to patients receiving optimal care.

TABLE 4. OUD TREATMENT PIPELINE<sup>19</sup>

Agent Name	Phase of Development	Description	Sponsor/Developer
CAM2038 (buprenorphine)	<ul style="list-style-type: none"> <li>Currently undergoing FDA review with a decision expected by December 26, 2018</li> <li>Also in development for the treatment of pain in opioid-tolerant patients</li> </ul>	Monthly and weekly SC injectable formulations of buprenorphine	Braeburn Pharmaceuticals

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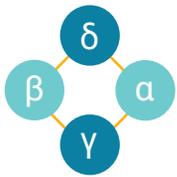
$\gamma$

$\beta$

# THE POTENTIAL OF PI3K INHIBITION

$\alpha$

$\delta$



**PI3K isoforms and their distinct functions**



**Potential inhibition of the tumor and its microenvironment**



**The importance of targeted therapies**

For more information on PI3K inhibition  
please visit [PI3Kinhibition.com](http://PI3Kinhibition.com)

# PARP Inhibitors in Ovarian Cancer:

## Management Considerations

The enzyme poly (ADP-ribose) polymerase (PARP) is responsible for repairing damaged deoxyribonucleic acid (DNA).<sup>1</sup> Blocking PARP with the use of new therapeutic options, PARP inhibitors, may prevent cancer cells from repairing their damaged DNA.<sup>2</sup> In 40% to 50% of epithelial ovarian cancers, genetic mutations are responsible for the homologous recombination DNA repair pathway.<sup>3</sup> The identification of germline and somatic mutations involved in the homologous recombination DNA repair pathway aids in guiding decision-making on when PARP inhibitors are indicated and which PARP inhibitor is most appropriate.<sup>3</sup>



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Magellan Method

There are currently three U.S. Food and Drug Administration (FDA)-approved PARP inhibitors on the market:

- 1 Lynparza (olaparib)
- 2 Rubraca (rucaparib)
- 3 Zejula (niraparib)

The three available treatments differ in terms of approved indications for use, formulations, and clinical data supporting their safety and efficacy. To date, there have been no head-to-head comparisons among the PARP inhibitor class.<sup>2</sup>

### Current Treatment Landscape

#### *Lynparza*

1 Lynparza is indicated for the maintenance treatment of adult patients with

recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.<sup>4</sup>

2 Lynparza is also approved for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with at least three lines of chemotherapy.<sup>4</sup>

3 Additionally, Lynparza is approved for the treatment of patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.<sup>4</sup>

» In patients who have hormone receptor (HR)-positive breast cancer, prior treatment should include endocrine therapy or patients should be considered inappropriate for endocrine therapy.<sup>4</sup>

#### *Rubraca*

1 Rubraca is approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.<sup>5</sup>

2 Rubraca is also indicated for the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal

cancer who have been treated with at least two chemotherapies.<sup>5</sup>

### Zejula

Zejula is approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.<sup>6</sup>

### Companion Diagnostics

It is recommended that all patients undergo testing to detect the presence of possible mutations; however, not all patients undergo genetic mutation testing.<sup>3</sup> All three treatments are now FDA-approved for use, regardless of a patient's BRCA status, in patients with advanced epithelial ovarian cancer (Table 1).<sup>4-6</sup>

### Future Directions

Ongoing clinical trials are evaluating the use of PARP inhibitors in combination with other therapies; however, data is not yet available to aid in the determination as to whether PARP inhibitors should be used in earlier lines of therapy.<sup>7</sup> Examples of such combinations include Keytruda (pembrolizumab) in combination with Zejula. In a phase I/II TOPACIO clinical trial (N=62), combination therapy produced complete or partial responses in 25% of patients with ovarian cancer compared to response rates of <5% in similar patients treated with PARP inhibitor monotherapy and 11% in patients treated with Keytruda monotherapy.<sup>8</sup>

As noted in their respective FDA labeling, PARP inhibitors have been approved by the FDA for patients with ovarian cancer that carries mutations in the BRCA genes and whose disease

Tests	Drugs	Diagnostic Detections
BRCAAnalysis CDx (Myriad Genetics)	Lynparza (olaparib)	Deleterious or suspected deleterious germline BRCA variants in protein coding regions and intron/exon boundaries of BRCA1 and BRCA2 genes in patients with ovarian cancer who are or may become eligible for treatment with Lynparza
FoundationFocus CDxBRCA (Foundation Medicine)	Rubraca (rucaparib)	Deleterious germline BRCA gene mutations in tumor tissue of patients with ovarian cancer
BRCAAnalysis CDx (Myriad Genetics)	Zejula (niraparib)	Germline BRCA mutations in patients with ovarian cancer who are likely to benefit most from treatment with Zejula

\*These are the only FDA-approved companion diagnostics for the ovarian cancer indications. The FDA-approved labeling for these products specifically states that these are the tests that accompany these drugs; however, there are also unapproved genetic tests available that are not noted in this table. Information available at [www.fda.gov](http://www.fda.gov).

Manufacturer	PARP Inhibitor	Maintenance Dosing
AstraZeneca	Lynparza (olaparib)	300 mg BID <sup>a</sup>
Clovis Oncology	Rubraca (rucaparib)	600 mg BID <sup>a</sup>
Tesaro	Zejula (niraparib)	300 mg BID <sup>a</sup>

Note: See "Additional Considerations" section on the next page, as prescribers should anticipate that more than 50% of patients will undergo dose reduction in the first month.

<sup>a</sup>BID = twice daily.

Information available at [www.fda.gov](http://www.fda.gov).

is platinum-sensitive.<sup>4-6</sup> Of note, PARP inhibitor monotherapy produces a response in <5% of patients whose ovarian cancer is platinum-resistant and BRCA mutation-free.<sup>8</sup> In the trial, Keytruda in combination with Zejula, 26% of evaluable patients with platinum-resistant ovarian cancer and wild-type

BRCA experienced remissions, and no severe or unexpected side effects were observed.<sup>8</sup> Additionally, a disease control rate of 67% was observed.<sup>9</sup>

A second study (N=34), MEDIOLA, evaluated combination treatment with Lynparza and the immune checkpoint inhibitor, Imfinzi (durvalumab), in patients with platinum-sensitive ovarian cancer.<sup>9</sup> The results of this study demonstrated an objective response rate of 72% and a disease control rate of 81%.<sup>9</sup> The results of these two studies are promising and highlight the potential for additional PARP inhibitor/immune checkpoint inhibitor combination studies in ovarian cancer and possibly other solid cancers, as well as the potential

**All three treatments are now FDA-approved for use, regardless of a patient's BRCA status, in patients with advanced epithelial ovarian cancer.**

for possible synergy between the two drug classes, based on observations from preclinical data and data from the two uncontrolled series.<sup>8,9</sup>

### Additional Considerations

Given the availability of three PARP inhibitors that share the indication for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy, some payers have begun to consider the possibility of selecting a preferred PARP inhibitor on their formularies. When evaluating which product will be the preferred agent on their formularies, payers consider a variety of factors, such as indications for use, safety and efficacy data, drug interactions, dosing schedules, and cost.<sup>3</sup> In clinical trials, treatment with

*When evaluating which product will be the preferred agent on their formularies, payers consider a variety of factors, such as indications for use, safety and efficacy data, drug-drug interactions, dosing schedules, and cost.*

all three drugs has demonstrated statistically significant progression-free survival improvement and impressive hazard ratios.<sup>10</sup>

Given the newly available information regarding the various PARP inhibitors, it is important that payers consider that pricing alone may not offer the most comprehensive view of the total cost of care for patients utilizing PARP inhibitors. Payers are encouraged to evaluate

real-world utilization of PARP inhibitors among their membership to determine the actual total cost of care for each PARP inhibitor on their formulary. This real-world cost information, along with the previously mentioned factors, including indications for use, safety and efficacy data, drug-drug interactions and dosing schedules, should be considered when evaluating PARP inhibitors for selected of a preferred forumarly agent.

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# Influence Key Decision-Makers

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# HOW CAN YOU HELP PROTECT PATIENTS AGAINST LOSS OF VISION?

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

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

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

### INDICATIONS AND IMPORTANT SAFETY INFORMATION

#### INDICATIONS

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

#### CONTRAINDICATIONS

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

#### WARNINGS AND PRECAUTIONS

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

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

#### ADVERSE REACTIONS

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

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

<sup>†</sup>After an initial monthly dosing period for certain indications.

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

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

**REGENERON**

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08/2016  
US-PMA-12565



**EYLEA**<sup>®</sup>  
(aflibercept) Injection  
For Intravitreal Injection



**BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION**

FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.

**1 INDICATIONS AND USAGE**

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

**2 DOSAGE AND ADMINISTRATION**

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

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

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

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

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

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

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

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

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

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

After injection, any unused product must be discarded.

**3 DOSAGE FORMS AND STRENGTHS**

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

**4 CONTRAINDICATIONS**

EYLEA is contraindicated in patients with

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

**5 WARNINGS AND PRECAUTIONS**

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

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

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

**6 ADVERSE REACTIONS**

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

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

**6.1 Clinical Trials Experience.** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**8 USE IN SPECIFIC POPULATIONS**

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

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

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

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

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

**17 PATIENT COUNSELING INFORMATION**

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

**REGENERON**

Manufactured by:  
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June 2016

# Multiple Myeloma:

## Future Directions in Treatment

**M**ultiple myeloma is a form of cancer that is characterized by the proliferation of cancerous plasma cells in the bone marrow.<sup>1-3</sup> In a healthy individual, plasma cells are responsible for the production of antibodies that help the body fight infection. In patients with multiple myeloma, aberrant plasma cells produce abnormal antibody proteins, commonly referred to as monoclonal immunoglobulin, monoclonal protein (M-protein), M-spike, or paraprotein. The proliferation of aberrant cells in the bone marrow may result in significant skeletal damage, including osteolytic lesions, osteopenia, or pathologic fractures.<sup>1-3</sup> The growth of myeloma cells is also associated with kidney failure.<sup>1-3</sup>



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Translational Genomics Research Institute, City of Hope Cancer Center  
Chief Medical Officer, International Myeloma Foundation

Confirmation of a diagnosis of multiple myeloma is crucial, as it may be commonly confused with the premalignant stages of myeloma, including monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), which are generally asymptomatic and do not require treatment.<sup>1,4</sup> It is estimated that at least 3% of the population over the age of 50 years have MGUS and this premalignant stage of disease progresses to multiple myeloma or a related malignancy at a rate of 1% per year.<sup>5</sup> SMM is considered an intermediate but more advanced premalignant stage of disease. While it is also asymptomatic, SMM may be identified clinically.<sup>2-5</sup>

Establishment of MGUS is the first step in the development of multiple myeloma. Although the precipitating event is unclear, MGUS appears to be the result of an abnormal plasma cell response to antigenic stimulation, resulting in the production of monoclonal immunoglobulin by the plasma cell clone. The conversion of MGUS to multiple myeloma occurs as a result of further insult to the plasma cell clone, either through the accumulation of additional genetic abnormalities or through changes in the bone marrow microenvironment.<sup>1,5</sup> Once this conversion occurs, patients generally become symptomatic due to the infiltration of plasma cells into the bone or other organs, or due to kidney damage from the presence of excess light chains.<sup>1,5</sup>

### Clinical Presentation of Multiple Myeloma<sup>2,3,6</sup>

- 1 Bone pain with lytic lesions (may be more pronounced in spine or chest)
- 2 Increased total serum protein concentration
- 3 Presence of monoclonal protein in urine or serum
- 4 Hematologic abnormalities (e.g., unexplained anemia, thrombocytopenia, leukopenia)
- 5 Hypercalcemia, with or without associated symptoms
- 6 Acute renal failure
- 7 Infections
- 8 Other signs or symptoms of malignancy (e.g., fatigue, weakness, weight loss)

- 
- 9 Nephrotic syndrome due to concurrent immunoglobulin light chain amyloidosis (less common)

While multiple myeloma is relatively rare, accounting for just 1% of all cancers, it is the second most common hematological malignancy, accounting for approximately 10% of total cases.<sup>1</sup> In the Western world, the age-adjusted incidence of multiple myeloma is approximately five cases per 100,000, with a median age at diagnosis of 66 to 70 years.<sup>1</sup> Although extremely rare, cases of multiple myeloma have occurred in individuals younger than 30 years of age, with a reported frequency ranging from 0.02% to 0.3%.<sup>1</sup> Several factors are believed to increase an individual's risk of developing multiple myeloma, including increased age, male gender, black race, family history, and personal history of MGUS.<sup>1,6</sup>

Unfortunately, there is currently no cure for multiple myeloma, and it accounts for approximately 20% of all deaths from hematological malignancies, as well as 2% of deaths from all cancers.<sup>5</sup> Fortunately, there have been significant advancements in the treatment of multiple myeloma, leading to improvements in survival over the past two decades. Prior to 2000, the median survival in patients with relapsed multiple myeloma was reported to be 12 months; after 2000, the median survival doubled to 24 months.<sup>1,5</sup> These improvements in survival rates are likely attributable to the availability of autologous hematopoietic stem cell transplantation, as well as immunomodulatory drugs and proteasome inhibitors. According to data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, the five-year relative survival increased to 49% for the time period of 2005 to 2011 compared to 27% in 1987 to 1989.<sup>1</sup> Notably, the first proteasome inhibitor (bortezomib [Velcade]) was approved in 2003 and the first immunomodulatory drugs (thalidomide [Thalomid], lenalidomide [Revlimid]) for multiple myeloma were approved in 2006, which may have contributed to the improvement in survival observed during this period.<sup>1,5</sup>

## Treatment of Multiple Myeloma

### Initial Treatment Approach

Although there is no general consensus in terms of which regimen is preferred, it is recommended that all patients diagnosed with multiple myeloma receive induction therapy.<sup>4,7</sup> The duration of induction therapy is dependent on the regimen selected, as well as whether the patient will receive a subsequent autologous hematopoietic stem cell transplant. For patients eligible for stem cell transplant, it is recommended that induction therapy be administered for two to four months prior to stem cell collection to reduce the tumor cell burden in the bone marrow and peripheral blood, as well as to reduce symptoms and end organ damage.<sup>7</sup> For patients who are not eligible for stem cell transplant who are receiving induction therapy with lenalidomide plus dexamethasone, it is generally recommended that patients continue treatment until disease progression or significant toxicity.<sup>7</sup> For patients receiving induction therapy with an alkylator- or bortezomib-based therapy, it is recommended that treatment be administered for 12 to 18 months, followed by observation until disease progression.<sup>4,7</sup>

Following induction therapy, patients who are eligible for stem cell transplant have several treatment options, including early or delayed autologous stem cell transplant or high-dose chemo-

therapy followed by allogeneic stem cell transplant.<sup>4,7</sup> For patients receiving autologous stem cell transplant, the early transplant strategy involves administration of high-dose chemotherapy followed by one or two autologous stem cells transplants. Conversely, the delayed transplant strategy involves continued therapy, typically with the same induction regimen, until the first relapse, at which time the patient would receive autologous stem cell transplant. Available data suggest that the early and delayed transplant strategies result in similar survival rates.<sup>4,7</sup> Allogeneic stem cell transplant does offer a potential cure; however, it is not generally preferred as a first-line option because it is associated with high early mortality rates and significant side effects.<sup>4,7</sup>

While induction therapy followed by early or delayed autologous stem cell transplant is the preferred treatment approach, selection of early or delayed transplant is dependent on factors such as patient preference, patient age (early strategy preferred as patients approach 70 years of age), comorbidities, and response and tolerability to initial chemotherapy, among others.<sup>4,7</sup>

### Approach to Relapsed or Refractory Disease

Virtually all patients who survive initial treatment will experience relapse and require additional treatment.

*Unfortunately, there is currently no cure for multiple myeloma, and it accounts for approximately 20% of all deaths from hematological malignancies, as well as 2% of deaths from all cancers.*

*A variety of novel immunotherapeutic approaches are currently under investigation, including the use of novel monoclonal antibodies, small molecules, vaccines, adoptive T-cell therapies, and chimeric antigen receptor (CAR-T) therapies.*

Patients with relapsed or refractory disease may receive stem cell transplant, a rechallenge of the chemotherapy regimen that was previously administered, or treatment with a new regimen. A second stem cell transplant should be considered in patients who have already undergone an autologous stem cell transplant who experienced a durable effect with

the first transplant.<sup>7-8</sup>

For patients who are ineligible for stem cell transplant, there are several treatment options available; however, it is important to note that the duration and quality of response with each subsequent treatment is diminished relative to the initial response.<sup>9-10</sup> In one study that was completed prior to the U.S. Food

and Drug Administration (FDA) approval and widespread use of immunomodulatory drugs and proteasome inhibitors, the investigators found that the median event-free survival was 10 months with the initial regimen, seven months with the second regimen, and decreased to just three months by the sixth regimen. Following the incorporation of bortezomib and lenalidomide into standard clinical practice for the initial treatment of multiple myeloma, the median progression-free survival increased to two years in patients who did not receive stem cell transplant and four years in patients who received stem cell transplant plus maintenance therapy. Following the incorporation of newer regimens containing carfilzomib (Kyprolis), elotuzumab (Empliciti), daratumumab (Darzalex), or ixazomib (Ninlaro) into clinical practice, the median progression-free survival following first relapse has significantly improved to two years.<sup>9,10</sup> Treatment selection for relapsed or refractory multiple myeloma should take into consideration the previous

**TABLE 1. TREATMENT OPTIONS FOR RELAPSED OR REFRACTORY MULTIPLE MYELOMA<sup>10-19</sup>**

Drug Name and Date of FDA Approval	FDA-Approved Indication	Clinical Notes
Revlimid (lenalidomide) 12/2005	• Treatment of multiple myeloma in combination with dexamethasone and maintenance therapy in multiple myeloma following autologous hematopoietic stem cell transplantation	<ul style="list-style-type: none"> <li>• Oral administration</li> <li>• Used alone or in combination with dexamethasone</li> <li>• Overall response rate of 60% when given in combination with dexamethasone</li> </ul>
Pomalyst (pomalidomide) 2/2013	• Treatment of multiple myeloma in patients who have received at least two prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy	<ul style="list-style-type: none"> <li>• Oral administration</li> <li>• Overall response rate of 60% when given in combination with dexamethasone</li> <li>• Overall response rate of 30% in lenalidomide-refractory disease and 25% in lenalidomide- and bortezomib-refractory disease</li> </ul>
Thalomid (thalidomide) 7/1998	• Treatment of newly diagnosed multiple myeloma in combination with dexamethasone	<ul style="list-style-type: none"> <li>• Oral administration</li> <li>• Has been studied in relapsed or refractory multiple myeloma alone and in combination with other agents (e.g., dexamethasone)</li> <li>• Less effective with less favorable safety profile compared to lenalidomide and pomalidomide</li> <li>• Overall response rate of 46% when given in combination with dexamethasone</li> </ul>
Velcade (bortezomib) 5/2003	• Treatment of multiple myeloma	<ul style="list-style-type: none"> <li>• IV or subcutaneous administration</li> <li>• Overall response rates of 65% when given as part of combination therapy regimen (e.g., dexamethasone, dexamethasone plus lenalidomide or thalidomide, etc.)</li> </ul>

(CONT.) TABLE 1. TREATMENT OPTIONS FOR RELAPSED OR REFRACTORY MULTIPLE MYELOMA<sup>10-19</sup>

Drug Name and Date of FDA Approval	FDA-Approved Indication	Clinical Notes
Kyprolis (carfilzomib) 7/2012	<ul style="list-style-type: none"><li>• Treatment of relapsed or refractory multiple myeloma in combination with dexamethasone or with lenalidomide plus dexamethasone in patients who have received one to three prior lines of therapy</li></ul>	<ul style="list-style-type: none"><li>• IV administration</li><li>• Second-generation selective proteasome inhibitor</li><li>• Associated with improved progression-free survival and overall survival compared to bortezomib and carfilzomib</li><li>• Overall response rates &gt;85% when given in combination with lenalidomide and dexamethasone following one prior therapy</li></ul>
Ninlaro (ixazomib) 11/2015	<ul style="list-style-type: none"><li>• Treatment of multiple myeloma</li></ul>	<ul style="list-style-type: none"><li>• Oral administration</li><li>• Overall response rates &gt;75% when given in combination with lenalidomide and dexamethasone following one to three prior therapies</li></ul>
Farydak (panobinostat) 2/2015	<ul style="list-style-type: none"><li>• Treatment of multiple myeloma in combination with bortezomib and dexamethasone in patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent</li></ul>	<ul style="list-style-type: none"><li>• Oral administration</li><li>• Improvement in progression-free survival and median duration of response compared to bortezomib plus dexamethasone alone; no differences in survival (data not yet mature)</li><li>• Significant safety concerns; increased incidence of cardiac death in clinical trials</li></ul>
Darzalex (daratumumab) 11/2015	<p>Treatment of multiple myeloma:</p> <ul style="list-style-type: none"><li>• In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant</li><li>• In combination with dexamethasone plus lenalidomide or bortezomib in patients who have received at least one prior therapy</li><li>• In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor</li><li>• As monotherapy in patients who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent, or patients who are double-refractory</li></ul>	<ul style="list-style-type: none"><li>• IV administration</li><li>• Monoclonal antibody targeting CD38</li><li>• Overall response rates &gt;90% when given in combination with lenalidomide plus dexamethasone and &gt;80% when given in combination with bortezomib plus dexamethasone</li></ul>
Empliciti (elotuzumab) 11/2015	<ul style="list-style-type: none"><li>• Treatment of multiple myeloma in combination with lenalidomide and dexamethasone in patients who have received one to three prior therapies</li></ul>	<ul style="list-style-type: none"><li>• IV administration</li><li>• Monoclonal antibody targeting SLAMF7</li><li>• Overall response rates &gt;75% and improved overall survival (91% at one year) when given in combination with lenalidomide plus dexamethasone</li></ul>

Micromedex. Red Book Online. 2018.

regimens that the patient has received, as well as the duration and quality of response achieved with each previous regimen.<sup>9-10</sup> The most commonly used strategies would be a doublet regimen or triplet regimen including one to two novel agents with a steroid. Table 1 outlines the available treatment options for patients with relapsed or refractory disease.

### Future Directions

Given the significant improvements in clinical outcomes achieved with the recently approved monoclonal antibodies, there continues to be a great deal of focus on the development of biologics for the treatment of multiple myeloma in the pharmaceutical pipeline. A variety of novel immunotherapeutic approaches are currently under investigation, including the use of novel monoclonal antibodies,

small molecules, vaccines, adoptive T-cell therapies, and chimeric antigen receptor (CAR-T) therapies.<sup>20-21</sup>

#### Isatuximab

Isatuximab is an anti-CD38 monoclonal antibody being studied for the treatment of relapsed or refractory multiple myeloma as part of a combination regimen. In Phase Ib data presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting, treatment with isatuximab plus pomalidomide and dexamethasone was found to have an acceptable safety profile in patients with relapsed or refractory disease who had received two or more prior therapies, including lenalidomide and a proteasome inhibitor.<sup>22</sup> For all study cohorts combined, the overall response rate was 65.3%, with a response rate of 74.9% for the cohort that received the 10 mg/

kg dose, which was the dose selected for an expansion cohort.<sup>22</sup> Furthermore, patients who were refractory to lenalidomide achieved a response rate of 60%.<sup>22</sup> The mean duration of response was 36 weeks and the median time to first response was 4.3 weeks.<sup>22</sup>

There are two ongoing Phase III trials, IKEMA (N=325) and IMROZ (N=425), that will evaluate the efficacy of isatuximab in combination with carfilzomib and dexamethasone in patients who have received one to three prior treatments (IKEMA) and in combination with bortezomib, lenalidomide, and dexamethasone in newly diagnosed patients who are ineligible for stem cell transplant.<sup>23</sup>

#### Selinexor

Selinexor is a first-in-class, oral selective inhibitor of nuclear export (SINE inhibitor). Selinexor exerts its pharmaco-

*Although multiple myeloma accounts for approximately 1% of all cancers in the U.S., it is estimated that the costs associated with it are among the highest.*

logic effect by binding with and inhibiting the XPO1 nuclear export protein, leading to the accumulation of tumor suppression proteins in the cell nucleus, ultimately resulting in the selective induction and apoptosis of cancer cells.<sup>24</sup> Part two of the single-arm Phase IIb STORM study (N=78) evaluated treatment with selinexor plus dexamethasone in heavily pretreated patients with penta-refractory disease. The primary endpoint of the study was met, with an overall response rate of 25.4% for patients treated with selinexor, which included two complete responses and 29 partial or very good partial responses in patients with penta-refractory disease.<sup>25</sup>

Selinexor has been granted the Orphan Drug and Fast Track designations for multiple myeloma and the manufacturer indicated that it plans to submit a New Drug Application to the FDA in the second half of 2018, requesting accelerated approval.<sup>24</sup>

#### **Bb2121**

Bb2121 is a second-generation B-cell matura BCMA-targeted CAR-T therapy being studied for the treatment of multiple myeloma. In the ongoing Phase I CRB-401 study (N=21) presented at the American Society of Hematology (ASH) Annual Meeting in 2017, treatment with bb2121 was evaluated in a patient population that had received a median of seven prior therapies.<sup>26</sup> In the Phase I study, complete remission was achieved in 56% of patients.<sup>26</sup> Treatment was gen-

erally well-tolerated, with an objective response rate of 94% and a very good partial response rate or better of 89%. Furthermore, after 40 weeks of follow-up, the median progression-free survival had not yet been reached and the progression-free survival rate at nine months was 71%.<sup>26</sup> In terms of safety, cytokine release syndrome was observed in 71% of patients treated with bb2121; however, the majority of cases were grade 1 or 2.<sup>26</sup>

Recently the manufacturer announced that it has amended the protocol of the phase I CRB-401 study to increase the dose range of CAR-T cells and increase subject enrollment.<sup>27</sup> The manufacturer announced that it has amended the protocol of the phase II KarMMa trial as well, by also increasing the dose range of CAR-T cells and increasing the enrollment target, citing the totality of clini-

cal data.<sup>27</sup> The FDA granted bb2121 the breakthrough therapy designation based on the preliminary data from the CRB-401 study.<sup>26</sup>

#### **Impact on Managed Care**

Although multiple myeloma accounts for approximately 1% of all cancers in the U.S., it is estimated that the costs associated with it are among the highest.<sup>28</sup> One study found that the costs of treatment also increase with each subsequent line of treatment; during the first line, the total all-cause per member per month (PMPM) costs were \$22,527. In the second line, costs increased to \$35,266 PMPM and in the third line, \$47,417 PMPM.<sup>29</sup> In addition, as the treatment paradigm shifts from autologous hematopoietic stem cell transplant and chemotherapy to more targeted immunotherapies, including CAR-T therapy, the pharmacy-related costs associated with the treatment of multiple myeloma may increase dramatically. It is important that payers focus on the effectiveness of new treatments and the clinical benefit they may provide in delaying or even preventing relapse.<sup>28,29</sup> The current trend is that, barring toxicity, most patients are going to be treated indefinitely with relapsed myeloma, which has a clear long-term economic burden. There is a potential for minimal residual disease testing to be able to limit that long-term therapy, but studies are ongoing to determine the feasibility of that approach.

*As the treatment paradigm shifts from hematopoietic stem cell transplant and chemotherapy to more targeted immunotherapies, including CAR-T therapy, the pharmacy-related costs associated with the treatment of multiple myeloma may increase dramatically.*

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# Multiple Sclerosis:

## Current Pipeline Treatments and Their Impact

**M**ultiple sclerosis is the most common immune-mediated disorder of the central nervous system and is characterized by inflammation, demyelination, and degenerative changes.<sup>1,2</sup> The inflammation that occurs as a result of an immune response causes damage to the myelin surrounding the nerve fibers, as well as the nerve fibers themselves. When this damage to the myelin or nerve fibers occurs, signal transmission within the central nervous system is impaired. In addition, the damage to the myelin and nerve fibers leads to the development of scar tissue over time.<sup>1,2</sup>

central nervous system. Magnetic resonance imaging (MRI) is used to confirm diagnosis, with typical findings that include hyperintense lesions within the white matter in characteristic locations (i.e., periventricular, cortical or juxtacortical, infratentorial, and spinal cord).<sup>1,2</sup>

Individuals with multiple sclerosis typically present as young adults with at least one episode of central nervous system dysfunction with at least partial resolution. Although there are no clinical findings that are specific to multiple sclerosis, common manifestations may include sensory symptoms of the limbs or face, unilateral vision loss, motor weakness, gait disturbance, or issues with balance. Depending on the individual patient, initial presenting symptoms may be consistent with either a single lesion or multiple lesions.<sup>1,2</sup>

According to recent estimates, there are approximately 450,000 individuals living with multiple sclerosis in the U.S.<sup>1</sup> Multiple sclerosis affects women approximately three times more frequently than men, and typically presents in early adulthood.<sup>1</sup> While Caucasians are affected more commonly than other races, some studies suggest that African Americans may have a more active and rapidly progressive disease course.<sup>1</sup> The vast majority, approximately 85% to 90%, of individuals with multiple sclerosis initially exhibit a relapsing-remitting pattern of disease. If left untreated, the majority of patients who initially present with relapsing-remit-

There are two core subtypes of the disease, relapsing-remitting and progressive multiple sclerosis, and these subtypes can be further sub-categorized based on the pattern and course of disease. These additional subtypes include clinically isolated syndrome, relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, and secondary progressive multiple sclerosis.<sup>1,2</sup> Most individuals with multiple sclerosis experience periods of relapse and remission of their neurological symptoms, with gradual worsening or progression of disease becoming more common over time.<sup>1,2</sup> Clinical events are typically associated with areas of inflammation in the



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*Approximately 10% to 15% of individuals with relapsing-remitting disease will experience steady progression of symptoms over time, with some individuals experiencing inflammatory activity clinically or on MRI, which is referred to as primary progressive disease.*

ting disease will transition to a pattern of progressive worsening, with few if any relapses, referred to as secondary progressive disease.<sup>1</sup> Approximately 10% to 15% of individuals with relapsing-remitting disease will experience steady progression of symptoms over time, with some individuals experiencing inflammatory activity clinically or on MRI, which is referred to as primary progressive disease.<sup>1</sup> The neurologic disability that occurs with multiple sclerosis varies significantly and the individual impact varies according to several factors, including symptom severity, the frequency of relapse, the rate of worsening, and residual disability.<sup>1,2</sup>

Prior to the development of disease modifying therapies, approximately 50% of patients diagnosed with relapsing-remitting disease would progress to secondary progressive disease within 10 years of diagnosis, and 80% to 90% would progress within 25 years of diagnosis. Furthermore, approximately 50% of patients would lose the ability to ambulate unaided within 15 years after diagnosis.<sup>1</sup>

Compared to other chronic disease states, individuals with multiple sclerosis have reduced ratings in health, vitality, and physical functions, and they report experiencing limitations in social roles as a result of their disease. Findings from a study evaluating burden of disease based on data from the Medical Expenditure Panel Survey suggest that the annual direct healthcare costs for individuals with multiple sclerosis

were \$24,327 higher than for the general population.<sup>3</sup> In addition, individuals with multiple sclerosis were more likely to be unemployed, spent more time in bed, and lost an average of 10 quality-adjusted life years.<sup>3</sup> Although the course of disease is highly variable, the average life expectancy may be reduced by six to seven years in individuals with multiple sclerosis.<sup>1,3-4</sup>

### **Current Treatment Landscape**

According to consensus treatment guidelines from the American Academy of Neurology (AAN), the treatment approach to multiple sclerosis should take into consideration patient values and preferences with respect to route of administration, lifestyle, efficacy, anticipated adverse effects, tolerability, and cost.<sup>1,4</sup> The AAN emphasizes the impor-

tance of setting realistic expectations for patients initiating disease-modifying treatment, informing patients that the goal of therapy is to reduce the frequency of relapses and the development of new MRI lesion activity and not to improve symptoms. Given the demonstrated efficacy of disease-modifying therapies in reducing relapse rates, improving MRI measures of disease activity, and preventing or delaying the progression of disability, the AAN recommends initiating disease-modifying therapy in all patients with relapsing forms of the disease. For patients with primary progressive disease, ocrelizumab is the only disease-modifying therapy that has demonstrated efficacy in altering disease progression in individuals who remain ambulatory. There is currently no data evaluating the benefits of disease-modifying therapy in patients with primary progressive disease who are nonambulatory.<sup>4</sup>

Unfortunately, none of the available disease-modifying therapies are completely effective in preventing relapse or the development of brain lesions.<sup>4</sup> If a patient experiences breakthrough disease activity with their current regimen, switching to a new medication with a different mechanism of action may be appropriate. Table 1 includes an overview of the U.S. Food and Drug Administration (FDA)-approved disease-modifying therapies for the treatment of multiple sclerosis.

*According to consensus treatment guidelines from the American Academy of Neurology, the treatment approach to multiple sclerosis should take into consideration patient values and preferences with respect to route of administration, lifestyle, efficacy, anticipated adverse effects, tolerability, and cost.*

**TABLE 1. FDA-APPROVED DISEASE-MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS<sup>1,4-18</sup>**

Drug Name and Date of FDA Approval	Clinical Notes
Copaxone (glatiramer acetate) 12/1996	<ul style="list-style-type: none"> <li>Dosing: 20 mg SC daily or 40 mg SC three times weekly</li> <li>Available generically</li> <li>Pregnancy category B</li> <li>Clinical trial data: 29% relative reduction in relapse rate over 24 months compared to placebo (20 mg dose); 34% reduction in ARR at 12 months compared to placebo (40 mg dose)</li> </ul>
Avonex (interferon beta-1a) 5/1996	<ul style="list-style-type: none"> <li>Dosing: 30 mcg IM weekly</li> <li>Pregnancy category C</li> <li>Clinical trial data: 18% reduction in mean number of relapses per patient year compared to placebo</li> </ul>
Rebif (interferon beta-1a) 3/2002	<ul style="list-style-type: none"> <li>Dosing: 22 mcg or 44 mcg SC three times weekly</li> <li>Pregnancy category C</li> <li>Clinical trial data (44 mcg dose): 33.2% reduction in mean number of relapses per person at 24 months compared to placebo</li> </ul>
Betaseron, Extavia (interferon beta-1b) 7/1993	<ul style="list-style-type: none"> <li>Dosing: 0.25 mg SC every other day</li> <li>Pregnancy category C</li> <li>Clinical trial data: 34% reduction in ARR over two years compared to placebo</li> </ul>
Plegridy (peginterferon beta-1a) 8/2014	<ul style="list-style-type: none"> <li>Dosing: 125 mcg SC every two weeks</li> <li>Pregnancy category C</li> <li>Clinical trial data: 36% reduction in ARR at 48 weeks compared to placebo</li> </ul>
Tecfidera (dimethyl fumarate) 3/2013	<ul style="list-style-type: none"> <li>Dosing: 240 mg orally twice daily</li> <li>Pregnancy category C</li> <li>Clinical trial data: 44% reduction in ARR at two years compared to placebo; 49% reduction in proportion of patients experiencing relapse within two years compared to placebo</li> </ul>
Gilenya (fingolimod) 9/2010	<ul style="list-style-type: none"> <li>Dosing: 0.5 mg orally once daily</li> <li>Pregnancy category C</li> <li>Clinical trial data: 48% to 54% reduction in ARR at two years compared to placebo</li> </ul>
Aubagio (teriflunomide) 9/2012	<ul style="list-style-type: none"> <li>Dosing: 7 mg or 14 mg orally once daily</li> <li>Pregnancy category X</li> <li>Black box warning for hepatotoxicity and risk of teratogenicity</li> <li>Clinical trial data: 31% reduction in ARR over two years compared to placebo</li> </ul>
Lemtrada (alemtuzumab) 11/2014	<ul style="list-style-type: none"> <li>Dosing: 12 mg/day IV on five consecutive days, followed by 12 mg/day IV on three consecutive days 12 months later</li> <li>Pregnancy category C</li> <li>Generally reserved for patients with relapsing-remitting disease who have failed treatment with ≥2 prior therapies</li> <li>Black box warning for risk of autoimmunity, life-threatening infusion reactions, and malignancies; available only through restricted distribution under REMS program</li> <li>Clinical trial data: 49% to 55% reduction in ARR at two years compared to interferon beta-1a 44 mcg three times weekly</li> </ul>
Novantrone (mitoxantrone) 12/1987	<ul style="list-style-type: none"> <li>Dosing: 12 mg/m<sup>2</sup> IV every three months; maximum cumulative dose: 140 mg/m<sup>2</sup></li> <li>Available generically</li> <li>In addition to indication for relapsing-remitting disease, also indicated for progressive-relapsing and secondary progressive multiple sclerosis</li> <li>Black box warning for cardiotoxicity and secondary leukemia; long-term monitoring is required following discontinuation</li> <li>Clinical trial data: 66% reduction in ARR at two years compared to placebo</li> </ul>
Tysabri (natalizumab) 11/2004	<ul style="list-style-type: none"> <li>Dosing: 300 mg IV every 28 days</li> <li>Pregnancy category C</li> <li>Black box warning due to risk of PML; only available through restricted distribution under TOUCH Prescribing Program</li> <li>Clinical trial data: 68% reduction in ARR at two years compared to placebo</li> </ul>
Ocrevus (ocrelizumab) 3/2017	<ul style="list-style-type: none"> <li>Dosing: 600 mg IV every six months</li> <li>No pregnancy category assigned<sup>1</sup></li> <li>Clinical trial data (relapsing-remitting disease): 46% relative reduction in ARR compared to interferon beta-1a 44 mcg three times weekly</li> <li>Clinical trial data (primary progressive disease): 47% relative reduction in ARR compared to placebo</li> </ul>

<sup>1</sup>No pregnancy category assigned due to changes in FDA labeling procedures for pregnancy and lactation. Abbreviations: ARR = annualized relapse rate, IM = intramuscular, IV = intravenous, PML = progressive multifocal leukoencephalopathy, REMS = Risk Evaluation Mitigation Strategies, SC = subcutaneous

In addition to the disease-modifying therapies listed above, dalfampridine (Ampyra) was FDA-approved in January 2010 to improve walking in patients with multiple sclerosis, making it the first agent to be approved for the management of disease-related symptoms.<sup>19</sup> Despite its effect on ambulation, it is important to note that dalfampridine has no effect on the underlying disease or disease progression, and it should be used solely for symptomatic treatment. In clinical trials, a significantly greater proportion of patients treated with dalfampridine 10 mg twice daily were responders based on the timed 25-foot walk test, which was defined as any patient who showed faster walking speed for at least three visits out of a possible four during the double-blind period than the maximum value achieved in the five non-double-blind no treatment visits (four visits prior to the double-blind period and one visit after).<sup>19</sup>

## Multiple Sclerosis Pipeline

### *Siponimod*

Siponimod is an investigational, oral selective modulator of the sphingosine-1-phosphate (S1P) receptor that is currently being studied for the treatment of secondary progressive multiple sclerosis.<sup>20</sup> S1P receptors, which are commonly found on the surface of cells within the central nervous system, are responsible for causing the damage that drives loss of function in secondary progressive disease. Selective binding of the S1P receptor is thought to inhibit a subset of activated lymphocytes from migrating to sites of inflammation. By binding to the S1P receptors, siponimod may help reduce loss of physical and cognitive function.<sup>20</sup>

The Phase III EXPAND study (N=1,651) evaluated treatment with siponimod in patients with secondary progressive multiple sclerosis.<sup>21</sup> The study met its primary endpoint, with a reduction in the risk of disability progression of 21% for siponimod compared to placebo at month three.<sup>21</sup> Treatment with siponimod was also associated with a 26% reduction in the risk of six-month

confirmed disability progression and a 55% reduction in annualized relapse rate compared to placebo. In addition, patients treated with siponimod had 23% lower average change in brain volume and reduced lesion volume compared to patients who received the placebo, key secondary endpoints. There was no significant difference observed between groups in the timed 25-foot walk test. In terms of safety, treatment with siponimod was generally well-tolerated, with a safety profile similar to that of other S1P modulators, such as fingolimod. The serious adverse events that were observed more frequently in the siponimod treatment group included nervous system disorders and infections.<sup>21,22</sup>

If approved, siponimod may be the first disease-modifying therapy that has demonstrated the ability to delay disability progression in secondary progressive multiple sclerosis, including those patients who have reached a non-relapsing stage of disease, as well as a high level of disability. According to the manufacturer, a New Drug Application (NDA) submission to the FDA is planned for 2018.<sup>20</sup>

### *Ozanimod*

Ozanimod is an investigational, oral selective S1P-1 and S1P-5 receptor modulator that is currently being studied for the treatment of various immune-inflammatory diseases, including relapsing-remitting multiple sclerosis.<sup>23</sup> Similar to siponimod, by binding to the S1P-1 receptor, treatment with ozanimod may prevent activated lymphocytes from migrating to sites of inflammation, thereby reducing the circulating T and B lymphocytes that lead to anti-inflammatory activity.<sup>21,23</sup> In addition, ozanimod also binds the S1P-5 receptor, which is thought to activate specific cells within the central nervous system that lead to enhanced remyelination as well as prevention of synaptic defects, thereby preventing neurological damage.<sup>23</sup>

Data from the Phase III SUNBEAM and RADIANCE studies (N=2,659) was presented at the AAN Annual Meeting

in April 2018.<sup>24-25</sup> Both studies evaluated the efficacy and safety of ozanimod 1 mg or 0.5 mg orally compared to interferon beta-1a (Avonex) 30 mcg administered intramuscularly. In the SUNBEAM trial, patients treated with either dose of ozanimod experienced fewer relapses per year compared to those treated with interferon beta-1a (0.195 relapses, 0.210 relapses, and 0.338 relapses for ozanimod 1 mg, ozanimod 0.5 mg, and interferon beta-1a, respectively).<sup>24-25</sup> Similar results were also observed in the RADIANCE trial, which compared the efficacy of ozanimod and interferon beta-1a over 24 months.<sup>24-25</sup> Treatment with ozanimod 1 mg and 0.5 mg resulted in reductions in annualized relapse rate of 0.157 and 0.228, respectively, compared to 0.246 with interferon beta-1a. In terms of safety, treatment-related adverse events were reported more frequently in patients who received interferon beta-1a compared to ozanimod. Both treatment groups demonstrated a similar risk of infection; however, no serious opportunistic infections were reported during either study.<sup>24-25</sup>

In February 2018, the manufacturer of ozanimod reported that they received a Refusal to File letter from the FDA in response to the NDA that had been submitted. Specifically, the FDA determined that the nonclinical and clinical pharmacology sections in the NDA were not sufficient to permit a full review.<sup>23</sup> Industry analysts have speculated that the FDA will likely request two-year animal cancer carcinogenicity studies due to a new metabolite that was found at high levels in humans who received ozanimod.<sup>23</sup> Despite the regulatory setback, the manufacturer reports that it anticipates resubmitting the NDA to the FDA in 2019.<sup>26</sup>

## Impact on Managed Care

As mentioned previously, the health-care costs associated with the management of multiple sclerosis are even higher than what is incurred with other chronic disease states.<sup>3</sup> The AAN highlights the importance of early treatment initiation and medication adherence

in achieving optimal clinical outcomes with disease-modifying therapies. In addition, the clinical evidence supports the development of a treatment plan that is highly individualized, with no single disease-modifying therapy being optimal in all patients. By taking into consideration patient preferences and values in selecting therapy,

patients may be more likely to adhere to it. It is also important to note that over time, efficacy and tolerability of one disease-modifying therapy may diminish, precipitating the need to switch to another agent.<sup>4</sup> Payers should be cognizant of these unique treatment considerations when designing management strategies for disease-modifying thera-

pies in multiple sclerosis to ensure that patients do not face barriers to medication access that may adversely affect their disease management. In addition, medication adherence monitoring programs, including specialty medication management, should be considered.

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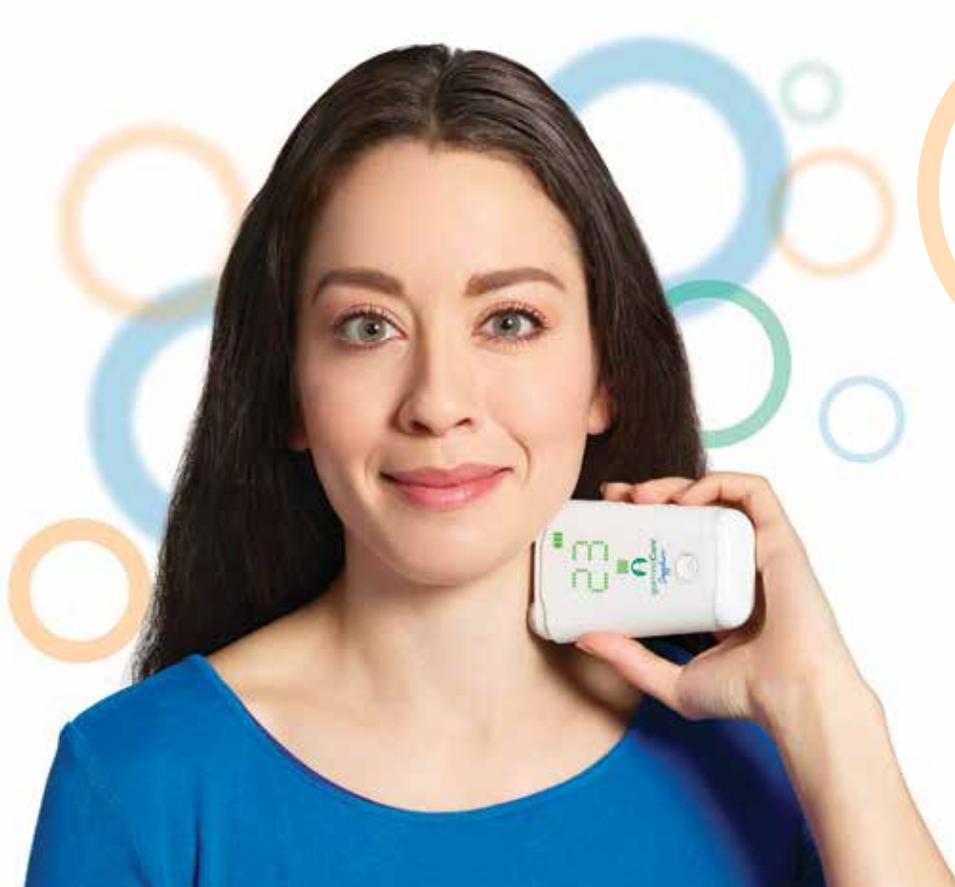


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  - Pediatric patients
  - Pregnant women
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- Patients should not use gammaCore if they:
  - Have a metallic device such as a stent, bone plate, or bone screw implanted at or near their neck
  - Are using another device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device (e.g., mobile phone)

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

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

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



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# Payer Perspectives on Botulinum Toxin Management for Therapeutic Use

**B**otulinum toxins are commonly used for cosmetic purposes; however, they are also clinically indicated for a variety of medical conditions related to neurological disorders. In the U.S., four preparations of botulinum toxin are commercially available: three formulations of botulinum toxin type A, and one formulation of botulinum toxin type B. However, U.S. Food and Drug Administration (FDA)-approved indications and dosing patterns vary by toxin product. Although these products are widely utilized, there is limited data regarding the clinical utilization and health plan management of these agents. While the relative priority of toxin management varies among health plans, many recognize the rising utilization and cost of these treatments and are challenged with determining how to appropriately manage this category. To identify potential opportunities for reducing the financial impact related to toxin management, an independent payer panel (PP) convened to discuss data on toxin utilization and costs, and challenges and opportunities for improved cost-effective toxin management.

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The panel was comprised of 10 health plan representatives: five medical and five pharmacy directors from commercial, Medicare, and Medicaid plans. PP participants were representative of integrated delivery networks (IDNs) and regional health plans recognized as organizations with the ability to implement innovative clinical management programs. PP participants discussed a range of strategies that, if implemented and enforced, could produce cost savings while retaining or improving clinical outcomes, and

maintaining patient and provider satisfaction. The following management strategies were identified by the PP as methods that health plans have or anticipate applying as tools to facilitate improved management of toxin utilization: prior authorizations (PAs), product preferencing, differential reimbursement, site-of-care (SOC) restrictions, and medical and pharmacy benefit access (Table 1).

**TABLE 1. PAYER PANEL (PP) PROPOSED STRATEGIES TO IMPROVE MANAGEMENT OF TOXIN UTILIZATION**

<p>Prior Authorizations (PAs)</p>	<ul style="list-style-type: none"> <li>• Each PP participant’s organization reported using the traditional PA and coverage determination process for toxins, but noted enforcement of these policies is relaxed.</li> <li>• Collectively, the PP did not support the off-label usage of these products and agreed toxins should be approved only for FDA-approved indications via the PA process.</li> </ul>
<p>Product Preferencing</p>	<ul style="list-style-type: none"> <li>• Health plans with medical pharmacy management strategies in place report utilizing non-indication-based product preferencing as a mainstay of existing toxin management strategies. <ul style="list-style-type: none"> <li>» This is, in large part, due to patient and provider preference for continuing the use of the same botulinum toxin product that the patient started on and the absence of economic evaluation of management options, as this therapeutic option may not be cost-saving.</li> </ul> </li> <li>• The PP discussed the challenges inherent in enforcing policies that support the utilization of preferred products for provider-administered therapies. <ul style="list-style-type: none"> <li>» Patients and providers request access to non-preferred products without engaging with the health plan clinical personnel regarding coverage policies.</li> </ul> </li> <li>• A product preferencing strategy must be supported by a PA process, enforced, and aligned with provider incentives to be successful. <ul style="list-style-type: none"> <li>» For example, PP participants discussed product preferencing policies that align the provider reimbursement fee schedule with coverage policies in a manner that supports usage of the plan-preferred products.</li> </ul> </li> </ul>
<p>Differential Reimbursement</p>	<ul style="list-style-type: none"> <li>• Approximately two-thirds of the PP stated that they reimburse equivalently across this class.</li> <li>• Alternatively, two payers explained that reimbursement is based on an average sales price (ASP) plus a percentage markup, which varies by product. Other PP participants indicated preferred products may be eligible for reimbursement at a higher rate.</li> <li>• However, among plans with differential reimbursement fee schedules, all reported providing incremental reimbursement increases for products that are most cost-effective for that plan, based on net cost, taking into consideration the product acquisition cost and discounts in the form of rebates.</li> </ul>
<p>Site-of-Care (SOC) Restrictions</p>	<ul style="list-style-type: none"> <li>• Three plans reported having SOC restrictions in place, which emphasize treatment in the more cost-effective sites of care (e.g., provider office vs. outpatient hospital).</li> <li>• One plan indicated a strategy that includes distribution channel restrictions, with a drug acquisition strategy mandating use of a specialty pharmacy to acquire the drug.</li> </ul>
<p>Medical and Pharmacy Benefit Access</p>	<ul style="list-style-type: none"> <li>• Of the plans represented at the PP, a majority stated that utilization of toxins is much higher under the medical benefit than the pharmacy benefit.</li> <li>• In discussion of the potential for enhanced management capabilities for drugs administered under the pharmacy benefit, payers noted a willingness, in some instances, to consider expanding coverage of toxins to both the pharmacy and medical benefit.</li> <li>• However, payer representatives were clear that they do not envision any changes to policy that would eliminate coverage through the medical benefit. <ul style="list-style-type: none"> <li>» PP members indicated that any shift away from the medical benefit would be met with resistance by providers as such a change would result in unnecessary workflow impacts, including increased administrative burden for provider offices and a reduction in provider revenues associated with the buy-and-bill acquisition method.</li> </ul> </li> </ul>

## *Institution of a policy guiding access by indication would not create an additional significant burden on the plan during the PA process.*

The PP stated that a comprehensive toxin management strategy would be beneficial, and that an optimal toxin clinical program strategy focused on cost containment must have the following components:

### **1. Product Access Guided by Indication**

All organizations represented in the PP noted having the ability to guide and restrict access by indication utilizing the traditional PA process. Institution of a policy guiding access by indication would not create an additional significant burden on the plan during the PA process. PP members suggested that this would logically be integrated into the PA process by adding the review of diagnosis, such as the International Classification of Diseases (ICD-10) code and other key variables such as National Drug Code, procedure code, and Healthcare Common Procedure Coding System (HCPCS) code. For some organizations, this would require edits be put into place within the PA system, likely implemented into the health plan claims processing and PA infrastructure in a manner that ensures the alignment of PA process with the toxin coverage policy, to support timely and accurate coverage determinations.

### **2. Additional Staffing Resources and Training**

Clinical staff reviewing PAs and making coverage determinations would need comprehensive training regarding the updated policies and changes and a list of all circumstances for appropriate approval or denial. Training updates would be necessary to accommodate

potential expanded indications for use or rationale for denial of use in investigational conditions. Most plans reported that additional data management/administrative resources would be needed as coverage determinations would likely require additional time to review as there will no longer be a blanket approval or a clear pathway to PA approval with few or no product selection criteria, i.e., the current "soft" PA approval. As mentioned previously, health plan data management system adjustments might require modifications to align with and facilitate claim analysis relative to revised criteria. If these changes are anticipated to result in a net cost savings, plans may be willing to dedicate additional resources necessary to support the execution of a more resource-intensive management strategy.

### **3. Physician Buy-In**

Plans anticipate the potential for substantial resistance from providers to a coverage policy that results in transitioning utilization toward other products. To mitigate provider pushback,

payers must implement a system that minimizes additional administrative workload for provider practices, as it aligns financial incentives for providers with updated policy and PA processes. One proposed strategy was the adjustment of the physician fee schedule to allow for incremental reimbursement of preferred product(s). Before implementation of a new management strategy and coverage policy, proactive provider engagement and acceptance are vital to ensure a smooth transition. To reach physicians throughout a plan's network, educational messaging regarding policy changes and addressing any nuances between the various products in this class must be undertaken in a manner that is thorough, systematic, and reinforced sufficiently to reach and resonate with providers.

### **4. Value-Based Contracting**

The PP participants indicated that health plans would likely view a well-structured medical pharmacy benefit contract as being of greater value and significance than one for the pharmacy benefit. This is largely due to the administration of the toxins within the provider office or outpatient settings.

### **5. Cost Savings**

PP members stated that any incremental cost savings will be attractive to plans looking to decrease overall costs. The more substantial the cost savings, the more motivated payers will be to implement and execute a management strategy.

*Proactive provider engagement and acceptance, before implementation of a new management strategy and coverage policy is vital to ensure a smooth transition.*

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The potential for a management strategy that yields cost savings is realized when evaluating the variations in toxin pricing and the corresponding unit size associated with each product. An additional management, and savings, opportunity may reside in managing the frequency of administration of the toxins.

During PP discussions, it was noted that many plans have begun to recognize that increasing toxin utilization across a growing number of conditions has a profound impact on health plan budgets. PP participants shared that although the toxin class has gone relatively unmanaged by payers, the need and opportunity to implement management strategies that improve the cost-effective treatment of patients is increasingly evident. The extent to which these strategies are utilized and enforced varies widely from plan to plan, with some PP participants noting that even in organizations with toxin management policies in place, there may be a relatively low level of policy enforcement.

In discussion of the opportunity associated with the previously examined medical pharmacy management strategies, payers noted several significant challenges remain. Among these were variations in the manner in which providers are reimbursed for toxin therapies. None of the plans represented at the PP reported accounting for different units of biological activity or dosing differences. Additionally, given that toxins are not interchangeable, there

***PP participants shared that although the toxin class has gone relatively unmanaged by payers, the need and opportunity to implement management strategies that improve the cost-effective treatment of patients is increasingly evident.***

are important differences in formulation, unit, and dosing differences that must be taken into account when considering products.

Toxins represent one of many classes in which payers are challenged to manage costs. While recognizing the importance of toxins to overall health plan finances, some plans were less focused on or somewhat unaware of potential solutions and implementation strategies for cost containment in this space. However, when discussing the opportunity to implement a cost-containment strategy, all payers viewed the option favorably, with the caveat that there is attention to workflow impact and there are strategies to assure provider support (e.g., educational resources are critical to successful implementation). The PP participants regarded current utilization and provider preference as the most influential drivers of payer motivation. The historically large market share of older botulinum toxins

challenges plans as they consider strategies for containing costs by shifting utilization to more cost-effective alternatives, while proceeding in a manner that minimizes provider/patient dissatisfaction. There is a growing awareness of the need for better management strategies, and the opportunities discussed by the PP could lead to better management of costs associated with botulinum toxins.

### **Disclosure**

*The panel discussion was sponsored by Ipsen Biopharmaceuticals, Inc. and facilitated by Magellan Rx Management.*

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<sup>a</sup>Level A recommendation for effectiveness signifies intervention should be offered.

<sup>b</sup>Based on WAC at maximum approved doses across all therapeutic indications.

<sup>c</sup>Coverage data are provided by Zitter Health Insights. Information presented here is not a guarantee of coverage. Coverage data believed to be accurate at time of update (Updated April 2018) but cannot be guaranteed. Individual cost and benefits design may vary. Please consult with individual plans. Ipsen Biopharmaceuticals, Inc. does not endorse any individual, commercial, Medicare Part D, or Medicaid plan.

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For adults with spasticity or cervical dystonia

# Consider Dysport®—because a long duration of response matters<sup>1</sup>



In clinical trials:

- Proven effective at reducing muscle tone at week 4 as assessed by the Modified Ashworth Scale (MAS) and Physician’s Global Assessment (PGA)
- The majority of patients in clinical studies were retreated between 12 - 16 weeks; however, some patients had a longer duration of response, ie 20 weeks

## PERCENTAGE OF PATIENTS HAVING DURATION OF RESPONSE OF AT LEAST 20 WEEKS

Adult Upper Extremity Spasticity	Adult Lower Extremity Spasticity
<b>10.9%</b> 16/147	<b>5.9%</b> 13/229



Repeat Dysport treatment should be administered when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection

## IMPORTANT SAFETY INFORMATION (continued)

### Contraindications

Dysport is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components; or in the presence of infection at the proposed injection site(s); or in patients known to be allergic to cow’s milk protein. Hypersensitivity reactions including anaphylaxis have been reported.

<sup>1</sup>Symptoms of spasticity can include abnormal increase in muscle tone and muscle spasm.

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on following pages.



*It's Time*

## IMPORTANT SAFETY INFORMATION (continued)

### Warnings and Precautions

#### Lack of Interchangeability Between Botulinum Toxin Products

The potency Units of Dysport are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products, and, therefore, units of biological activity of Dysport cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

#### Dysphagia and Breathing Difficulties

Treatment with Dysport and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant side effects occur, additional respiratory muscles may be involved. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

#### Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of Dysport.

#### Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

#### Intradermal Immune Reaction

The possibility of an immune reaction when injected intradermally is unknown. The safety of Dysport for the treatment of hyperhidrosis has not been established. Dysport is approved only for intramuscular injection.

### Most Common Adverse Reactions

**Adults with upper limb spasticity** ( $\geq 2\%$  and greater than placebo): nasopharyngitis, urinary tract infection, muscular weakness, musculoskeletal pain, dizziness, fall, and depression.

**Adults with lower limb spasticity** ( $\geq 5\%$  and greater than placebo): falls, muscular weakness, and pain in extremity.

**Adults with cervical dystonia** ( $\geq 5\%$  and greater than placebo): muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, musculoskeletal pain, dysphonia, injection site pain, and eye disorders.

**Pediatric patients with lower limb spasticity** ( $\geq 10\%$  and greater than placebo): upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, cough, and pyrexia.

## IMPORTANT SAFETY INFORMATION (continued)

### Drug Interactions

Co-administration of Dysport and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of botulinum toxin may be potentiated. Use of anticholinergic drugs after administration of Dysport may potentiate systemic anticholinergic effects, such as blurred vision. The effect of administering different botulinum neurotoxins at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by another administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of Dysport.

### Use in Pregnancy

Based on animal data, Dysport may cause fetal harm. There are no adequate and well-controlled studies in pregnant women. Dysport should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Pediatric Use

Based on animal data Dysport may cause atrophy of injected and adjacent muscles; decreased bone growth, length, and mineral content; delayed sexual maturation; and decreased fertility.

### Geriatric Use

In general, elderly patients should be observed to evaluate their tolerability of Dysport, due to the greater frequency of concomitant disease and other drug therapy. Subjects aged 65 years and over who were treated with Dysport for lower limb spasticity reported a greater percentage of fall and asthenia as compared to those younger (10% vs. 6% and 4% vs. 2%, respectively).

**To report SUSPECTED ADVERSE REACTIONS or product complaints**, contact Ipsen at 1-855-463-5127. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### References

1. Dysport® (abobotulinumtoxinA) [Prescribing Information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; September 2017.
2. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. *Neurology*. 2016;86:1818-1826.
3. AnalySource Online. <https://www.analysource.com>. Accessed May 16, 2018.

Please see Brief Summary of Full Prescribing Information on following pages.

 **Dysport**<sup>®</sup>  
(abobotulinumtoxinA)

*It's Time*

## DYSPORT® (abobotulinumtoxinA) for injection, for intramuscular use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

### BOXED WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of DYSPORT and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including upper limb spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to or lower than the maximum recommended total dose.

### INDICATIONS AND USAGE:

Dysport® (abobotulinumtoxinA) for injection is indicated for the treatment of:

- Spasticity in adult patients
- Adults with cervical dystonia
- Lower limb spasticity in pediatric patients 2 years of age and older.

**CONTRAINDICATIONS:** DYSPORT is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation; or infection at the proposed injection site(s). Hypersensitivity reactions have been reported, including anaphylaxis. This product may contain trace amounts of cow's milk protein. Patients known to be allergic to cow's milk protein should not be treated with DYSPORT.

### WARNINGS AND PRECAUTIONS

**Lack of Interchangeability between Botulinum Toxin Products:** The potency Units of DYSPORT are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

**Spread of Toxin Effect:** Post-marketing safety data from DYSPORT and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life-threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including upper limb spasticity in children and approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than the maximum recommended total dose.

**Dysphagia and Breathing Difficulties:** Treatment with DYSPORT and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised. Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post-marketing reports of serious breathing difficulties, including respiratory failure. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

**Pre-existing Neuromuscular Disorders:** Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of DYSPORT.

**Human Albumin and Transmission of Viral Diseases:** This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

**Intradermal Immune Reaction:** The possibility of an immune reaction when injected intradermally is unknown. The safety of DYSPORT for the treatment of hyperhidrosis has not been established. DYSPORT is approved only for intramuscular injection.

### ADVERSE REACTIONS

**Cervical Dystonia (CD):** DYSPORT exposure data in 446 CD patients in 7 studies; two were randomized, double-blind, single treatment, placebo-controlled studies with subsequent optional open-label treatment in which dose optimization (250 to 1000 Units per treatment) over the course of 5 treatment cycles was allowed. Population: Caucasian (99%); median age 51 (range 18–82 years); (87%) less than 65 years of age; 58.4% women. In placebo-controlled trials the most common adverse reactions (>5%) reported in patients receiving DYSPORT 500 Units were muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, musculoskeletal pain, dysphonia, injection site pain and eye disorders (consisting of blurred vision, diplopia, and reduced visual acuity and accommodation). Other than injection site reactions, most adverse reactions became noticeable about one week after treatment and lasted several weeks. The rates of adverse reactions were higher in the combined controlled and open-label experience than in the placebo-controlled trials. Two patients (<1%) experienced adverse reactions leading to withdrawal and one experienced disturbance in attention, eyelid disorder, feeling abnormal and headache, and one patient experienced dysphagia. Most commonly reported adverse reactions  $\geq 5\%$  and greater than placebo) in patients who received DYSPORT 500 Units (N=173) vs. placebo (N=182), respectively were: **Any Adverse Reaction** (61%, 51%); **General disorders and administration site conditions** (30%, 23%), Injection site discomfort (13%, 8%), Fatigue (12%, 10%), Injection site pain (5%, 4%); **Musculoskeletal and connective tissue disorders** (30%, 18%), Muscular weakness (16%, 4%), Musculoskeletal pain (7%, 3%), **Gastrointestinal disorders** (28%, 15%), Dysphagia (15%, 4%), Dry mouth (13%, 7%); **Nervous system disorders** (16%, 13%), Headache (11%, 9%); **Infections and infestations** (13%, 9%); **Respiratory, thoracic and mediastinal disorders** (12%, 8%), Dysphonia (6%, 2%); **Eye disorders** [vision blurred, diplopia, visual acuity, reduced, eye pain, eyelid disorder, accommodation disorder, dry eye, eye pruritus] (7%, 2%). In a randomized, multiple fixed-dose study, the common adverse reactions (dose divided between two muscles—sternocleidomastoid and splenius capitis) for patients who received Placebo or DYPOR dose of either 250 Units, 500 Units, 1000 Units, respectively were: **Any Adverse Event** (30%, 37%, 65%, 83%); Dysphagia (5%, 21%, 29%, 39%); Dry mouth (10%, 21%, 18%, 39%); Muscular weakness (0%, 11%, 12%, 56%); Injection site discomfort (10%, 5%, 18%, 22%); Dysphonia (0%, 0%, 18%, 28%); Facial paresis (0%, 5%, 0%, 11%); and Eye disorders [vision blurred, diplopia, visual acuity, reduced, eye pain, eyelid disorder, accommodation disorder, dry eye, eye pruritus] (0%, 0%, 6%, 17%).

**Injection Site Reactions:** Injection site discomfort and injection site pain were common adverse reactions following DYSPORT administration.

**Less Common (<5%) Reported Adverse Reactions During Double-Blind Phase of Clinical Trials:** **Breathing Difficulty** reported by ~ 3% DYSPORT patients vs 1% of placebo patients, consisted mainly of dyspnea. The median time to onset from last dose of DYSPORT was approximately one week; median duration was approximately three weeks. Other adverse reactions (<5%) in the DYSPORT 500 Units group vs. placebo, respectively included dizziness (3.5%, 1%), and muscle atrophy (1%, 0%).

**Laboratory Findings:** Patients treated with DYSPORT exhibited a small increase from baseline (0.23 mol/L) in mean blood glucose relative to placebo-treated patients. This was not clinically significant among patients in the development program but could be a factor in patients whose diabetes is difficult to control.

**Electrocardiographic Findings:** ECG measurements were only recorded in a limited number of patients in an open-label study without a placebo or active control. This study showed a statistically significant reduction in heart rate compared to baseline, averaging about three beats per minute, observed thirty minutes after injection.

### Spasticity in Adults

**Injection Site Reactions** (e.g., pain, bruising, haemorrhage, erythema/haematoma etc.) have occurred following administration.

### Upper Limb Spasticity in Adults

In double-blind studies, the most common adverse reactions observed ( $\geq 2\%$ ) in any DYSPORT dose group: 500 Units (N=197), 1000 Units (N=194) and more frequently than Placebo (N=279), respectively were: **Infections and infestations:** Nasopharyngitis (4%, 1%, 1%), Urinary tract infection (3%, 1%, 2%), Influenza (1%, 2%, 1%), Infection (1%, 2%, 1%); **Musculoskeletal and connective tissue disorders:** Muscular weakness (2%, 4%, 1%), Pain in extremity (0%, 2%, 1%), Musculoskeletal pain (3%, 2%, 2%), Back pain (1%, 2%, 1%); **Nervous system disorders:** Headache (1%, 2%, 1%), Dizziness (3%, 1%, 1%), Convulsion (2%, 2%, 1%), Syncope (1%, 2%, 0%), Hypoaesthesia (0%, 2%, <1%), Partial seizures (0%, 2%, 0%); **General disorders and administration site conditions:** Fatigue (2%, 2%, 0%), Asthenia (2%, 1%, <1%); **Injury, poisoning and procedural complications:** Fall (2%, 3%, 2%), Injury (2%, 2%, 1%), Contusion (1%, 2%, <1%); **Gastrointestinal disorders:** Diarrhea (1%, 2%, <1%), Nausea (2%, 1%, 1%), Constipation (0%, 2%, 1%); **Investigation:** Blood triglycerides increased (2%, 1%, 0%); **Respiratory, thoracic and mediastinal disorders:** Cough (1%, 2%, 1%); **Vascular disorders:** Hypertension (1%, 2%, <1%); **Psychiatric disorders:** Depression (2%, 3%, 1%)

**Less Common Adverse Reactions:** In a pooled analysis of clinical studies, adverse reactions (<2%) reported in DYSPORT treatment groups included dysphagia 0.5%, gait disturbance 0.5%, hypertonia 0.5%, and sensation of heaviness 0.3%.

### Lower Limb Spasticity in Adults

Of the population exposed to DYSPORT (N=255), 89% Caucasian, 66% male, and median age was 55 years (range 23–77 years).

The most common adverse reactions ( $\geq 5\%$ ) in any DYSPORT dose group were falls, muscular weakness, and pain in extremity. Muscular weakness was reported more frequently in women (10%) treated with 1500 units of DYSPORT vs. men (5%). Falls were reported more frequently in patients  $\geq 65$  years of age. In a double-blind study, the most common adverse reactions

## DYSPO<sup>®</sup> (abobotulinumtoxinA) for injection, for intramuscular use Brief Summary of full Prescribing Information (cont.)

observed ( $\geq 2\%$ ) in any DYSPO<sup>®</sup> dose group: 1000 Units (N=127), 1500 Units (N=128) and more frequently than Placebo (N=130), respectively were: **Musculoskeletal and connective tissue:** Muscular weakness (2%, 7%, 3%), Pain in extremity (6%, 6%, 2%) Arthralgia (4%, 2%, 1%), Back pain (3%, 0%, 2%); **Injury, poisoning and procedural complications:** Fall (9%, 6%, 3%), Contusion (2%, 0%, 0%), Wrist fracture (2%, 0%, 0%); **Nervous system disorders:** Headache (0%, 3%, 1%), Epilepsy/Convulsion/Partial seizure/Status Epilepticus (4%, 1%, 2%); **Infections and infestations:** Upper respiratory tract infection (2%, 1%, 1%); **General disorders and administration site conditions:** Fatigue (1%, 4%, 0%), Asthenia (2%, 1%, 1%), Influenza-like illness (2%, 0%, 0%), Edema peripheral (2%, 0%, 0%); **Investigations:** Alanine aminotransferase increased (2%, 0%, 1%); **Gastrointestinal disorders:** Constipation (0%, 2%, 1%), Dysphagia (2%, 1%, 1%); **Psychiatric disorders:** Depression (2%, 3%, 0%), Insomnia (0%, 2%, 0%); **Vascular disorders:** Hypertension (2%, 1%, 1%).

### **Lower Limb (unilateral or bilateral) Spasticity in Pediatric Patients (2 to 17 years of age; cerebral palsy)**

In a double-blind study, the most common adverse reactions observed ( $\geq 4\%$ ) and reported more frequently than placebo, in patients who received placebo (N=79), Unilateral DYSPO<sup>®</sup> 10 units/kg (N=43), Unilateral DYSPO<sup>®</sup> 15 units/kg (N=50), Bilateral DYSPO<sup>®</sup> 20 units/kg (N=37), or Bilateral DYSPO<sup>®</sup> 30 units/kg (N=30), respectively were: **Infections and infestations:** Nasopharyngitis (5%, 9%, 12%, 16%, 10%), Upper respiratory tract infection (13%, 9%, 20%, 5%, 10%), Influenza (8%, 0%, 10%, 14%, 3%), Pharyngitis (8%, 5%, 0%, 11%, 3%), Bronchitis (3%, 0%, 0%, 8%, 7%), Rhinitis (4%, 5%, 0%, 3%, 3%), Varicella (1%, 5%, 0%, 5%, 0%), Ear infection (3%, 2%, 4%, 0%, 0%), Respiratory tract infection viral (0%, 5%, 2%, 0%, 0%), Gastroenteritis viral (0%, 2%, 4%, 0%, 0%); **Gastrointestinal disorders:** Vomiting (5%, 0%, 6%, 8%, 3%), Nausea (1%, 0%, 2%, 5%, 0%); **Respiratory, thoracic and mediastinal disorders:** Cough (6%, 7%, 6%, 14%, 10%), Oropharyngeal pain (0%, 2%, 4%, 0%, 0%); **General disorders and administration site conditions:** Pyrexia (5%, 7%, 12%, 8%, 7%); **Musculoskeletal and connective tissue:** Pain in extremity (5%, 0%, 2%, 5%, 7%), Muscular weakness (1%, 5%, 0%, 0%, 0%); **Nervous system disorders:** Convulsion/Epilepsy (0%, 7%, 4%, 0%, 7%)

**Postmarketing Experience:** Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post-approval use of DYSPO<sup>®</sup>: vertigo, photophobia, influenza-like illness, amyotrophy, burning sensation, facial paresis, hypoesthesia, erythema, and excessive granulation tissue. Hypersensitivity reactions including anaphylaxis have been reported.

**Immunogenicity:** As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products in this class may be misleading.

**Cervical Dystonia:** About 3% of subjects developed antibodies (binding or neutralizing) over time with DYSPO<sup>®</sup> treatment.

### **Spasticity in Adults**

**Upper Limb Spasticity:** From 230 subjects treated with DYSPO<sup>®</sup> and tested for the presence of binding antibodies, 5 subjects were positive at baseline and 17 developed antibodies after treatment. Among those 17 subjects, 10 subjects developed neutralizing antibodies. An additional 51 subjects from a separate repeat-dose study were tested for the presence of neutralizing antibodies only. None of the subjects tested positive. In total, from the 281 subjects treated in the long-term studies and tested for the presence of neutralizing antibodies, 3.6% developed neutralizing antibodies after treatment. In the presence of binding and neutralizing antibodies to DYSPO<sup>®</sup> some patients continue to experience clinical benefit.

**Lower Limb Spasticity:** From 367 subjects treated with DYSPO<sup>®</sup> and tested for the presence of binding antibodies, 4 subjects were positive at baseline and 2 developed binding antibodies after treatment. No subjects developed neutralizing antibodies. An additional 85 subjects from two separate studies were tested for the presence of neutralizing antibodies only. One subject tested positive for the presence of neutralizing antibodies. In total, from the 452 subjects treated in with DYSPO<sup>®</sup> and tested for the presence of neutralizing antibodies, 0.2% developed neutralizing antibodies after treatment.

**Lower Limb Spasticity in Pediatric Patients:** From 226 subjects treated with DYSPO<sup>®</sup> and tested for the presence of binding antibodies, 5 subjects previously receiving botulinum toxins were positive at baseline and 9 patients developed binding antibodies after injections. Among those 9 subjects, 3 subjects developed neutralizing antibodies, while one subject developed neutralizing antibodies from the 5 subjects testing positive for binding antibodies at baseline who previously received botulinum toxin injections. From a separate repeat-dose study, 203 subjects were tested for the presence of neutralizing antibodies. Two subjects were positive for neutralizing antibodies at baseline and 5 subjects developed neutralizing antibodies after treatments. In total, from the 429 patients tested for the presence of neutralizing antibodies, 2.1% developed neutralizing antibodies after treatment. In the presence of binding and neutralizing antibodies to DYSPO<sup>®</sup>, some patients continued to experience clinical benefit.

### **DRUG INTERACTIONS**

No formal drug interaction studies have been conducted with DYSPO<sup>®</sup>. Patients treated concomitantly with botulinum toxins and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents) should be observed closely because the effect of the botulinum toxin may be potentiated. Use of anticholinergic drugs after administration of DYSPO<sup>®</sup> may potentiate systemic anticholinergic effects such as blurred vision. The effect of administering different botulinum neurotoxin products at the same time or

within several months of each other is unknown. Excessive weakness may be exacerbated by another administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of DYSPO<sup>®</sup>.

### **USE IN SPECIFIC POPULATIONS**

**Pregnancy:** There are no adequate and well-controlled clinical studies with DYSPO<sup>®</sup> in pregnant women. DYSPO<sup>®</sup> should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. DYSPO<sup>®</sup> produced embryo-fetal toxicity in relation to maternal toxicity when given to pregnant rats and rabbits at doses lower than or similar to the maximum recommended human dose (MRHD) of 1000 Units on a body weight (Units/kg) basis.

**Lactation:** There are no data on the presence of DYSPO<sup>®</sup> in human or animal milk, the effects on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DYSPO<sup>®</sup> and any potential adverse effects on the breastfed infant from DYSPO<sup>®</sup> or from the underlying maternal condition.

**Females and Males of Reproductive Potential: Infertility (Females)** In rats, DYSPO<sup>®</sup> produced adverse effects on mating behavior and fertility.

### **Pediatric Use**

**Cervical Dystonia and Upper Limb Spasticity:** Safety and effectiveness in pediatric patients have not been established.

**Lower Limb Spasticity in Pediatric Patients:** The safety and effectiveness of DYSPO<sup>®</sup> injected into proximal muscles of the lower limb for the treatment of spasticity in pediatric patients, or with lower limb spasticity below 2 years of age, have not been established.

### **Geriatric Use**

#### **Cervical Dystonia**

There were insufficient numbers of patients aged 65 years and over in the clinical studies to determine whether they respond differently than younger patients. In general, elderly patients should be observed to evaluate their tolerability of DYSPO<sup>®</sup>, due to the greater frequency of concomitant disease and other drug therapy.

#### **Adult Spasticity**

##### **Upper Limb Spasticity**

Of the total number of subjects in placebo-controlled clinical studies of DYSPO<sup>®</sup>, 30% were  $\geq 65$  years of age, while 8% were  $\geq 75$  years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. 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.

##### **Lower Limb Spasticity**

Of the total number of subjects in placebo controlled clinical studies of DYSPO<sup>®</sup>, 18% (n = 115) were  $\geq 65$ , while 3% (n = 20) were  $\geq 75$ . Subjects aged  $\geq 65$  years who were treated with DYSPO<sup>®</sup> reported a greater percentage of adverse reactions as compared to younger subjects (46% vs. 39%). Fall and asthenia were observed with greater frequency in older subjects, as compared to those younger (10% vs. 6% and 4% vs. 2%, respectively).

**OVERDOSAGE:** Excessive doses of DYSPO<sup>®</sup> may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle. Symptomatic treatment may be necessary. Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis. There is no significant information regarding overdose from clinical studies.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 770-488-7100. More information can be obtained at <http://www.cdc.gov/ncidod/srp/drugs/drug-service.html>.

**Manufactured by:** Ipsen Biopharm Ltd. Wrexham, LL13 9UF, UK, U.S. License No. 1787

**Distributed by:** Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ 07920 and Galderma Laboratories, L.P., Fort Worth, TX 76177 USA

**Reference: 1.** Dysport<sup>®</sup> (abobotulinumtoxinA) [Prescribing Information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; September 2017.

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# PI3K Inhibitors:

## Pipeline and Therapeutic Advances

Over the last several years, dozens, if not hundreds, of new therapeutic targets have been identified for various cancer types. One such novel target is the phosphatidylinositol 3-kinase (PI3K) signaling pathway, which includes four Class I isoforms: alpha, beta, delta, and gamma ( $\alpha$ ,  $\beta$ ,  $\delta$ , and  $\gamma$ ).<sup>1</sup> The PI3K signaling pathway controls many of the cellular processes, including survival, proliferation, and metabolism.<sup>2</sup> The PI3K pathway is frequently dysregulated, often by genetic alterations and biochemical activation, and represents an attractive target for cancer treatment.<sup>1,3</sup> Currently, there are two U.S. Food and Drug Administration (FDA)-approved PI3K inhibitors, with dozens of investigational agents in development, including one novel, late-stage PI3K inhibitor: duvelisib.<sup>4-6</sup>

relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.<sup>4</sup> FL and SLL indications are based on overall response rate.<sup>4</sup> An improvement in patient survival or disease-related symptoms has not been established. The FDA labeling notes that Zydelig (idelalisib) is not indicated and is not recommended for first-line treatment of any patient, nor is it indicated or recommended in combination with bendamustine and/or rituximab for the treatment of FL.<sup>4</sup> The inhibitory activity of Zydelig (idelalisib) is against PI3K- $\delta$  kinase, which is expressed in normal and malignant B cells.<sup>4</sup> Zydelig (idelalisib) also inhibits several cell signaling pathways, including B-cell receptor (BCR) signaling and CXCR4 and CXCR5 signaling.<sup>4</sup> Zydelig (idelalisib) is available as 100 mg and 150 mg tablets, with a recommended maximum starting dose of 150 mg administered orally twice daily.<sup>4</sup>

### *Aliqopa (copanlisib)*

The second PI3K inhibitor to receive FDA approval was Aliqopa. Aliqopa is FDA-approved for the treatment of adult patients with relapsed FL who have received at least two prior systemic therapies.<sup>5</sup> The indication of adult patients with relapsed FL is based on overall response rate.<sup>5</sup> The inhibitory activity of Aliqopa is predominantly against PI3K- $\alpha$  and PI3K- $\delta$  isoforms expressed in malignant B cells.<sup>5</sup> Aliqopa also inhibits several key cell-signaling pathways, including BCR signaling, CXCL12 mediated chemotaxis of

### **Current Treatment Landscape** *Zydelig (idelalisib)*

The first PI3K inhibitor to receive FDA approval was Zydelig. Zydelig is FDA-approved for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would not be considered appropriate therapy due to other comorbidities; relapsed follicular B-cell non-Hodgkin's lymphoma (FL) in patients who have received at least two prior systemic therapies; and



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malignant B cells, and NF $\kappa$ B signaling in lymphoma cell lines.<sup>5</sup> Aliqopa is available as a 60 mg IV injection, and is administered as a one-hour IV infusion on days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off).<sup>5</sup>

## Late-Stage Pipeline

### Duvelisib

#### Mechanism of action

Duvelisib is an investigational PI3K inhibitor in late-stage development for the treatment of relapsed or refractory CLL/SLL and relapsed or refractory FL.<sup>6</sup> Duvelisib represents a first-in-class, oral dual inhibitor of PI3K- $\delta$  and PI3K- $\gamma$ , differentiating itself from the two existing products on the market.<sup>6</sup>

#### Fast Track Designation and Orphan Drug Designation

The FDA granted duvelisib fast track designation for patients with CLL or peripheral T-cell lymphoma (PTCL) who have received at least one prior therapy, and patients with FL who have received at least two prior therapies.<sup>6</sup> Duvelisib also received orphan drug designation in the U.S. for patients with CLL, SLL, and FL.<sup>6</sup>

#### Clinical Trial Data

The investigational treatment, duvelisib, is the first PI3K inhibitor to demonstrate efficacy as a monotherapy in a randomized phase III trial in patients

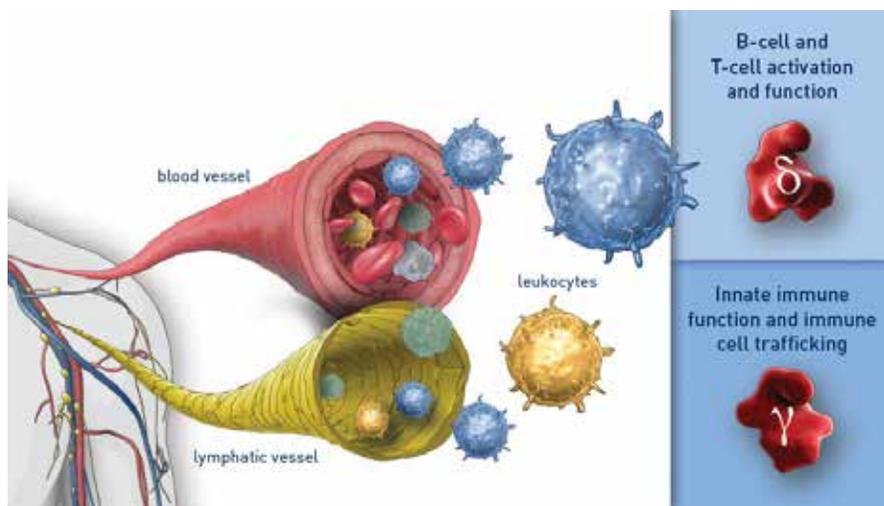


Image: Verastem Oncology. 2018. <http://www.verastem.com/focus/pi3k-inhibition>. Accessed 2018 Aug 2.

with relapsed or refractory CLL/SLL.<sup>6</sup> In addition, treatment with duvelisib monotherapy has shown significant clinical activity in patients with double-refractory FL.<sup>6</sup> The randomized phase III DUO study, which evaluated the safety and efficacy of duvelisib monotherapy in patients with relapsed or refractory CLL/SLL, demonstrated that treatment with duvelisib monotherapy offered significant efficacy and a consistent and manageable safety profile.<sup>6</sup> The study met its primary endpoint by demonstrating that treatment with duvelisib monotherapy achieved a statistically

significant improvement in progression-free survival (PFS) compared to ofatumumab in patients with relapsed or refractory CLL/SLL (median PFS of 13.3 months vs. 9.9 months, respectively; HR=0.52; P<0.0001), representing a 48% reduction in the risk of disease progression or death.<sup>6</sup>

Treatment with duvelisib was also studied in the phase II DYNAMO study in patients with indolent non-Hodgkin's lymphoma whose disease is double-refractory to both rituximab and chemotherapy or radioimmunotherapy.<sup>6</sup> This study also achieved its primary endpoint by demonstrating an objective response rate (ORR) of 46% (P<0.0001).<sup>6</sup> In the subset of patients enrolled in this study who had double-refractory FL (N=83), treatment with duvelisib demonstrated an ORR of 41%.<sup>6</sup>

There is also an ongoing phase II study: PRIMO, a multicenter, parallel cohort, open-label study of duvelisib in patients with relapsed or refractory PTCL.<sup>6</sup>

#### Chemotherapy-Free Treatment

Beyond its differentiated mechanism of action, duvelisib also differs from existing PI3K inhibitors in that it represents a single-agent,

***The investigational treatment, duvelisib, is the first PI3K inhibitor to demonstrate efficacy as a monotherapy in a randomized phase III trial in patients with relapsed or refractory CLL/SLL.***

## Beyond its differentiated mechanism of action, duvelisib also differs from existing PI3K inhibitors in that it represents a single-agent, chemotherapy-free treatment that has shown signs of clinical efficacy regardless of tumor burden or genetic alterations.

chemotherapy-free treatment that has shown signs of clinical efficacy regardless of tumor burden or genetic alterations.<sup>7</sup> Duvelisib treatment does not require planned hospitalization or infusions.<sup>7</sup>

### Duvelisib: Dual PI3K Inhibition

During the Verastem Oncology-hosted Analyst and Investor Day in May 2018, key opinion leaders in the hematologic oncology field led discussions about the current treatment landscape, the role of PI3K inhibitors in the treatment paradigm, and the need for new anticancer agents in this space.<sup>7</sup>

Some of the highlights from the presentations included the following:<sup>7</sup>

1 Brian Koffman, MDCM, DCFP, FCFP, DABFP, MSEd, physician, founder and president of the CLL Society, and CLL patient: "I believe that more targeted options are needed for relapsed patients and therapy should be matched to each individual's profile and preference."

2 Jennifer Brown, MD, PhD, director of the CLL Center of the Division of Hematologic Malignancies at the Dana-Farber Cancer Institute, and associate professor of medicine at Harvard Medical School: "While there are other, efficacious targeted therapies available, each comes with its own limitations ... Duvelisib has a novel mechanism

that is easily given with no infusions required. This may provide a benefit to older patients in the community, which represents the majority of the patients."

3 Ian Flinn, MD, PhD, director of the Blood Cancer Research Program at the Sarah Cannon Research Institute: "The clinical activity and durability of responses observed in the DYNAMO study, seen across highly refractory disease subtypes such as FL, highlight

the potential of this drug in lymphoid malignancies. These results were seen in patients who were refractory to both rituximab and chemotherapy, a specific population with unmet medical need. Additional options are needed for a physician's armamentarium in the treatment of chronic indolent lymphomas and leukemias and the sequential use of clinically manageable treatments may extend the period of disease control. Continued development of oral, targeted therapies, such as duvelisib, is necessary to address the medical unmet need. The DYNAMO and DUO results support duvelisib oral monotherapy as a potential new and convenient treatment option for previously treated CLL/SLL or FL patients."

### FDA Decision Timeline

The manufacturer, Verastem Oncology, submitted a new drug application (NDA) to the FDA in February 2018.<sup>6</sup> The NDA submission was supported by the results from the phase III DUO and phase II DYNAMO studies.<sup>6</sup> The FDA has assigned duvelisib a Prescription Drug User Fee Act date of action date of October 5, 2018.<sup>7</sup>

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PIPELINE DRUG LIST

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Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
sufentanil (Dsuvia)	AcelRx Pharmaceuticals Inc.	Moderate to severe pain in trauma and ambulatory care settings	SL	505(b)(2) NDA	11/2/18
oliceridine (Olinvo)	Trevena Inc.	Moderate to severe acute pain	IV	Breakthrough therapy; fast track	11/2/18
fluocinolone acetonide (Iluvien)	Alimera Sciences Inc.	DME	Intraocular	Orphan drug	11/5/18
pembrolizumab (Keytruda)	Merck & Co. Inc.	HCC, advanced	IV	Priority review	11/9/18
revefenacin	Theravance Biopharma Inc.	COPD	Inhaled	Submitted	11/13/18
rifamycin (Aemcolo)	Cosmo Pharmaceuticals NV	Travelers' diarrhea	Oral	Fast track; priority review; qualified infectious disease product	11/16/18
emapalumab	Novimmune	HLH	IV	Breakthrough therapy; orphan drug; priority review	11/20/18
larotrectinib	Loxo Oncology Inc., Bayer	Solid tumors harboring NTRK fusion proteins	Oral	Breakthrough therapy; orphan drug; priority review	11/26/18
amifampridine phosphate (Firdapse)	Catalyst Pharmaceuticals Inc.	LEMS	Oral	Breakthrough therapy; orphan drug; priority review	11/28/18
gilteritinib	Astellas Pharma Inc.	AML (FLT3+)	Oral	Fast track; orphan drug; priority review	11/29/18
bupivacaine hydrochloride (XaraColl)	Innocoll AG	Postsurgical pain	Surgical implantation	Submitted	11/30/18
epinephrine (Primatene Mist)	Amphastar Pharmaceuticals Inc.	Asthma	Inhaled	505(b)(2) NDA	November, 2018
Nestorone/ethinyl estradiol contraceptive vaginal ring	Allergan PLC	Contraception	Intravaginal	Submitted	Q4, 2018
rizatriptan VersaFilm (Rizaport)	IntelGenx Corp.	Migraine	Oral transmucosal	505(b)(2) NDA	Q4, 2018
tadalafil VersaFilm	IntelGenx Corp.	ED	Oral	Submitted	Q4, 2018
brexanolone	Sage Therapeutics	Postpartum depression	IV	Breakthrough therapy; priority review	12/19/18
solriamfetol	Jazz Pharmaceuticals PLC	Excessive sleepiness associated with narcolepsy or OSA	Oral	Orphan drug (narcolepsy indication)	12/20/18
SHP555 (prucalopride)	Shire Pharmaceuticals Group PLC	CIC	Oral	Submitted	12/21/18
EZN-2285 (calaspargase pegol)	Shire Pharmaceuticals Group PLC	ALL	IV	Submitted	12/21/18
baloxavir marboxil	Roche Holding AG	Influenza	Oral	Priority review	12/24/18
CAM2038 (buprenorphine)	Braeburn, Camurus	SUD	SC	505(b)(2) NDA; fast track	12/26/18
dexamethasone punctum plug (Dextenza)	Ocular Therapeutix Inc.	Ocular pain following ophthalmic surgery	Intraocular	Submitted	12/28/18
siponimod	Novartis AG	SPMS	Oral	Submitted	Q4, 2018 - Q1, 2019
itraconazole (SUBA-Itraconazole)	HedgePath Pharmaceuticals Inc.	BCC in patients with BCCNS	Oral	505(b)(2) NDA	Q4, 2018 - Q1, 2019

PIPELINE DRUG LIST CONT.

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
glasdegib	Pfizer Inc.	AML	Oral	Orphan drug; priority review	December, 2018
talazoparib	Pfizer Inc.	Breast cancer (BRCA+, HER2-, locally advanced or metastatic)	Oral	Submitted	December, 2018
tacrolimus, extended-release tablets (Envarsus XR)	Veloxis Pharmaceuticals A/S	Kidney transplant rejection (de novo)	Oral	Submitted	1/7/19
romosozumab (Evenity)	Amgen Inc.	Osteoporosis	SC	Submitted	1/11/19
cabozantinib (Cabometyx)	Exelixis Inc.	HCC (including secondary metastases)	Oral	Orphan drug	1/14/19
sacituzumab govitecan	Immunomedics Inc.	TNBC	IV	Breakthrough therapy; fast track	1/18/19
APL-130277 (apomorphine)	Sunovion	Parkinson's disease	Oral transmucosal	505(b)(2) NDA; fast track	1/29/19
cladribine (Mavenclad)	Merck KGaA	Relapsing MS	Oral	Fast track	1/30/19
ALKS 5461 (samidorphan/buprenorphine)	Alkermes PLC	MDD	SL	Fast track	1/31/19
iclaprim	Motif Bio PLC	ABSSSIs	IV	Fast track; qualified infectious disease product	2/14/19
ALXN1210 (ravulizumab)	Alexion Pharmaceuticals Inc.	PNH	IV, SC	Orphan drug; priority review	2/19/19
tagraxofusp (Elzonris)	Stemline Therapeutics Inc.	BPDCN	IV	Breakthrough therapy; orphan drug	2/25/19
loteprednolletabonate	Bausch & Lomb	Postoperative inflammation and pain after ocular surgery	Topical	505(b)(2) NDA	2/25/19
afamelanotide (Scenesse)	Clinuvel Pharmaceuticals Ltd.	EPP	Intradermal	Fast track; orphan drug	2/25/19
N8-GP (turoctocog alfa pegol)	Novo Nordisk	Hemophilia A	IV	Submitted	2/27/19
netarsudil/latanoprost (Roclatan)	Aerie Pharmaceuticals Inc.	Glaucoma	Topical	505(b)(2) NDA	3/14/19
bremelanotide	AMAG Pharmaceuticals Inc.	FSAD	SC	Submitted	3/22/19
mometasone furoate/olopatadine hydrochloride (Ryaltris)	Glenmark Pharmaceuticals Ltd.	Seasonal allergic rhinitis	Intranasal	505(b)(2) NDA	3/22/19
sotagliflozin (Zynquista)	Sanofi	T1DM	Oral	Submitted	3/26/19
metoclopramide (Gimoti)	Evoke Pharma Inc.	Acute and recurrent diabetic gastroparesis in women with diabetes mellitus	Intranasal	505(b)(2) NDA	4/1/19
aclidinium and formoterol (Duaklir Pressair)	Circassia Pharmaceuticals PLC	COPD	Inhaled	Submitted	4/1/19

Abbreviations: ABSSSIs = acute bacterial skin and skin structure infections, ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, BCC = basal cell carcinoma, BCCNS = basal cell carcinoma nevus syndrome, BPDCN = blastic plasmacytoid dendritic cell neoplasm, CIC = chronic idiopathic constipation, COPD = chronic obstructive pulmonary disease, DME = diabetic macular edema, ED = erectile dysfunction, EPP = erythropoietic protoporphyria, FLT3+ = FMS-like tyrosine kinase 3 mutation positive, FSAD = female sexual arousal disorder, HCC = hepatocellular carcinoma, HER2- = human epidermal growth factor receptor 2-, HLH = hemophagocytic lymphohistiocytosis, LEMS = Lambert-Eaton myasthenic syndrome, MDD = major depressive disorder, MS = multiple sclerosis, NDA = new drug application, NTRK = neurotrophic tropomyosin receptor kinase, OSA = obstructive sleep apnea, PNH = paroxysmal nocturnal hemoglobinuria, SC = subcutaneous, SL = sublingual, SPMS = secondary progressive multiple sclerosis, SUD = substance use disorder, T1DM = type 1 diabetes mellitus, TNBC = triple-negative breast cancer

**WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV**

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

**INDICATIONS AND USAGE**

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

**CONTRAINDICATIONS**

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

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

**WARNINGS AND PRECAUTIONS**

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

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

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

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

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

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

**ADVERSE REACTIONS**

**Clinical Trials Experience**

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

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

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

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

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

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

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

**ENDURANCE-2**

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

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

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

**ENDURANCE-3**

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

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

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

<sup>1</sup> DCV=daclatasvir

<sup>2</sup> SOF=sofosbuvir

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

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

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

**Laboratory Abnormalities**

**Serum bilirubin elevations**

Elevations of total bilirubin at least 2 times the upper limit of normal occurred in 3.5% of subjects treated with MAVYRET versus 0% in placebo; these elevations were observed in 1.2% of subjects across the Phase 2 and 3 trials. MAVYRET inhibits OATP1B1/3 and is a weak inhibitor of UGT1A1 and may have the potential to impact bilirubin transport and metabolism, including direct and indirect bilirubin. No subjects experienced jaundice and total bilirubin levels decreased after completing MAVYRET.

**DRUG INTERACTIONS**

**Mechanisms for the Potential Effect of MAVYRET on Other Drugs**

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

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

**Mechanisms for the Potential Effect of Other Drugs on MAVYRET**

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

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

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

**Established and Other Potential Drug Interactions**

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

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

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

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
<b>Antimycobacterials:</b>		
Rifampin	↓ glecaprevir ↓ pibrentasvir	Coadministration is contraindicated because of potential loss of therapeutic effect [see Contraindications].
<b>Ethinyl Estradiol-Containing Products:</b>		
Ethinyl estradiol-containing medications such as combined oral contraceptives	↔ glecaprevir ↔ pibrentasvir	Coadministration of MAVYRET may increase the risk of ALT elevations and is not recommended.
<b>Herbal Products:</b>		
St. John's wort ( <i>hypericum perforatum</i> )	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
<b>HIV-Antiviral Agents:</b>		
Atazanavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is contraindicated due to increased risk of ALT elevations [see Contraindications].
Darunavir Lopinavir Ritonavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is not recommended.
Efavirenz	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
<b>HMG-CoA Reductase Inhibitors:</b>		
Atorvastatin Lovastatin Simvastatin	↑ atorvastatin ↑ lovastatin ↑ simvastatin	Coadministration may increase the concentration of atorvastatin, lovastatin, and simvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Coadministration with these statins is not recommended.
Pravastatin	↑ pravastatin	Coadministration may increase the concentration of pravastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Reduce pravastatin dose by 50% when coadministered with MAVYRET.
Rosuvastatin	↑ rosuvastatin	Coadministration may significantly increase the concentration of rosuvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with MAVYRET at a dose that does not exceed 10 mg.
Fluvastatin Pitavastatin	↑ fluvastatin ↑ pitavastatin	Coadministration may increase the concentrations of fluvastatin and pitavastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Use the lowest approved dose of fluvastatin or pitavastatin. If higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment.
<b>Immunosuppressants:</b>		
Cyclosporine	↑ glecaprevir ↑ pibrentasvir	MAVYRET is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day.

↑ = increase; ↓ = decrease; ↔ = no effect

**Drugs with No Observed Clinically Significant Interactions with MAVYRET**

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

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

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

<p>background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.</p> <p><b>Data</b></p> <p><b>Glecaprevir</b></p> <p>Glecaprevir was administered orally to pregnant rats (up to 120 mg/kg/day) and rabbits (up to 60 mg/kg/day) during the period of organogenesis (gestation days (GD) 6 to 18, and GD 7 to 19, respectively). No adverse embryo-fetal effects were observed in rats at dose levels up to 120 mg/kg/day (53 times the exposures in humans at the recommended human dose (RHD)). In rabbits, the highest glecaprevir exposure achieved was 7% (0.07 times) of the exposure in humans at RHD. As such, data in rabbits during organogenesis are not available for glecaprevir systemic exposures at or above the exposures in humans at the RHD.</p> <p>In the pre/post-natal developmental study in rats, glecaprevir was administered orally (up to 120 mg/kg/day) from GD 6 to lactation day 20. No effects were observed at maternal exposures 47 times the exposures in humans at the RHD.</p> <p><b>Pibrentasvir</b></p> <p>Pibrentasvir was administered orally to pregnant mice and rabbits (up to 100 mg/kg/day) during the period of organogenesis (GD 6 to 15, and GD 7 to 19, respectively). No adverse embryo-fetal effects were observed at any studied dose level in either species. The systemic exposures at the highest doses were 51 times (mice) and 1.5 times (rabbits) the exposures in humans at the RHD.</p> <p>In the pre/post-natal developmental study in mice, pibrentasvir was administered orally (up to 100 mg/kg/day) from GD 6 to lactation day 20. No effects were observed at maternal exposures approximately 74 times the exposures in humans at the RHD.</p> <p><b>Lactation</b></p> <p><b>Risk Summary</b></p> <p>It is not known whether the components of MAVYRET are excreted in human breast milk, affect human milk production, or have effects on the breastfed infant. When administered to lactating rodents, the components of MAVYRET were present in milk, without effect on growth and development observed in the nursing pups [see <i>Data</i>].</p> <p>The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MAVYRET and any potential adverse effects on the breastfed child from MAVYRET or from the underlying maternal condition.</p> <p><b>Data</b></p> <p>No significant effects of glecaprevir or pibrentasvir on growth and post-natal development were observed in nursing pups at the highest doses tested (120 mg/kg/day for glecaprevir and 100 mg/kg/day for pibrentasvir). Maternal systemic exposure (AUC) to glecaprevir and pibrentasvir was approximately 47 or 74 times the exposure in humans at the RHD. Systemic exposure in nursing pups on post-natal day 14 was approximately 0.6 to 2.2 % of the maternal exposure for glecaprevir and approximately one quarter to one third of the maternal exposure for pibrentasvir.</p>	<p>Glecaprevir or pibrentasvir was administered (single dose; 5 mg/kg oral) to lactating rats, 8 to 12 days post parturition. Glecaprevir in milk was 13 times lower than in plasma and pibrentasvir in milk was 1.5 times higher than in plasma. Parent drug (glecaprevir or pibrentasvir) represented the majority (&gt;96%) of the total drug-related material in milk.</p> <p><b>Pediatric Use</b></p> <p>Safety and effectiveness of MAVYRET in children less than 18 years of age have not been established.</p> <p><b>Geriatric Use</b></p> <p>In clinical trials of MAVYRET, 328 subjects were age 65 years and over (14% of the total number of subjects in the Phase 2 and 3 clinical trials) and 47 subjects were age 75 and over (2%). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects. No dosage adjustment of MAVYRET is warranted in geriatric patients.</p> <p><b>Renal Impairment</b></p> <p>No dosage adjustment of MAVYRET is required in patients with mild, moderate or severe renal impairment, including those on dialysis.</p> <p><b>Hepatic Impairment</b></p> <p>No dosage adjustment of MAVYRET is required in patients with mild hepatic impairment (Child-Pugh A). MAVYRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B). Safety and efficacy have not been established in HCV-infected patients with moderate hepatic impairment. MAVYRET is contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to higher exposures of glecaprevir and pibrentasvir [see <i>Contraindications</i>].</p> <p><b>OVERDOSAGE</b></p> <p>In case of overdose, the patient should be monitored for any signs and symptoms of toxicities. Appropriate symptomatic treatment should be instituted immediately. Glecaprevir and pibrentasvir are not significantly removed by hemodialysis.</p> <p><b>PATIENT COUNSELING INFORMATION</b></p> <p>Advise the patient to read the FDA-approved patient labeling (Patient Information).</p> <p><b>Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV</b></p> <p>Inform patients that HBV reactivation can occur in patients coinfecting with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of hepatitis B virus infection [see <i>Warnings and Precautions</i>].</p> <p><b>Drug Interactions</b></p> <p>Inform patients that MAVYRET may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication or herbal products [see <i>Contraindications, Warnings and Precautions and Drug Interactions</i>].</p>	<p><b>Administration</b></p> <p>Advise patients to take MAVYRET recommended dosage (three tablets) once daily with food as directed. Inform patients that it is important not to miss or skip doses and to take MAVYRET for the duration that is recommended by the physician.</p> <p>If a dose is missed and it is:</p> <ul style="list-style-type: none"> <li>• Less than 18 hours from the usual time that MAVYRET should have been taken – advise the patient to take the dose as soon as possible and then to take the next dose at the usual time.</li> <li>• More than 18 hours from the usual time that MAVYRET should have been taken – advise the patient not to take the missed dose and to take the next dose at the usual time.</li> </ul> <p>Manufactured by AbbVie Inc., North Chicago, IL 60064 MAVYRET is a trademark of AbbVie Inc.</p> <p>© 2017 AbbVie Inc. All rights reserved. Ref: 03-B632 Revised: December, 2017</p> <p>46A-1937720 MASTER</p> <p style="text-align: right;">46A-1937974 <b>abbvie</b></p>
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Learn more at  
[WWW.MAVYRET.COM](http://WWW.MAVYRET.COM)

**MAVYRET**<sup>™</sup>  
glecaprevir/pibrentasvir  
100 mg/40 mg tablets

**FOR CHRONIC HCV**

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

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

**DON'T  
LOOK  
BACK**

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

### INDICATION<sup>1</sup>

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

### IMPORTANT SAFETY INFORMATION<sup>1</sup>

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

### CONTRAINDICATIONS<sup>1</sup>

MAVYRET is contraindicated:

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

### WARNINGS AND PRECAUTIONS<sup>1</sup>

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

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

### ADVERSE REACTIONS<sup>1</sup>

**Most common adverse reactions observed with MAVYRET:**

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

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

GT=genotype.

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