Fall 2016

HIV: Novel Approaches to Patient Care Optimization

PAH: The Role of Combination Therapies in Treatment

Melanoma: How New Treatments Influence Patient Management

LARCs: Encouraging Use When Clinically Appropriate

Magellan Rx Report

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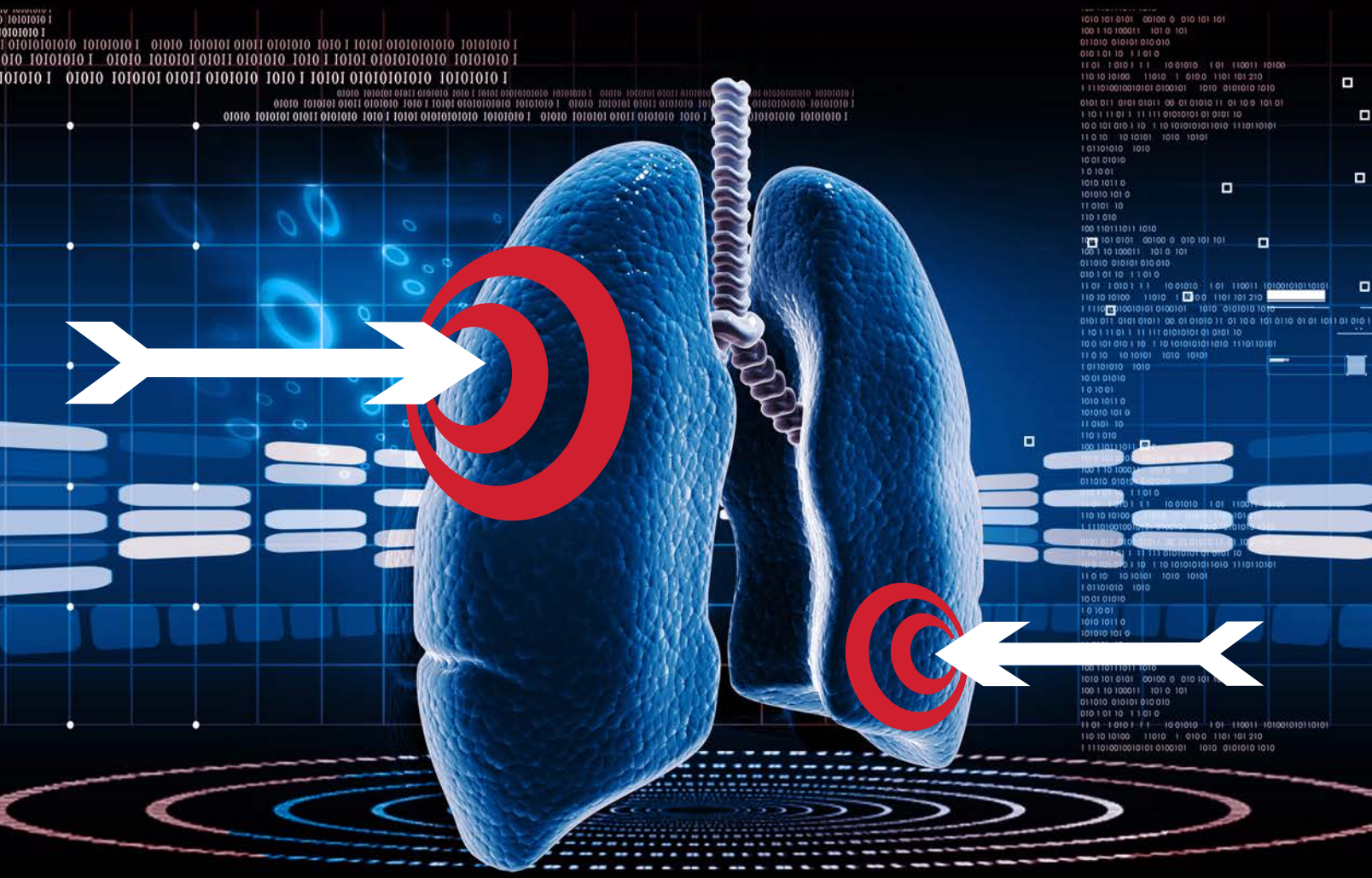

Asthma Management: Targeted Therapies May Bring Paradigm Change

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Welcome to the **Magellan Rx** Report

Published By

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ISSN: 2159-5372 10444M

Features

Trends

Maria Lopes

Dear Managed Care Colleagues,

Welcome to our fall issue of the *Magellan Rx™ Report*! As you are aware, managed care represents a dynamic, rapidly evolving health care environment, that not only exhibits challenges, but also presents opportunities for various stakeholders to develop solutions in order to manage these challenges. Amidst the recent therapeutic advances across a wide array of health conditions, payors continue to face mounting challenges surrounding the development of appropriate management strategies that address today's and tomorrow's population needs. At Magellan, we understand the importance of managing the fastest-growing, complex, high-cost areas of health care and seek to meet the evolving needs of our clients. For that reason, in this issue we have chosen to highlight several therapeutic areas that have experienced recent, notable changes to their respective treatment landscapes.

Prior to the advent of recent treatment innovations, many health conditions have been managed with traditional therapeutic approaches. A prime example of this is the management of asthma, which has typically hinged on the use of beta agonists and oral or inhaled anti-inflammatory agents to control the disease. The once traditional treatment landscape is now intersecting with new, innovative and potentially higher-priced, targeted therapies, requiring payors to develop effective strategies for managing the utilization of these drugs. In this issue, we explore the impact of new and emerging therapies on both clinical outcomes and treatment costs associated with this disease which is occurring with increasing prevalence.

No issue of the *Magellan Rx™ Report* would be complete without a focus on the management of more complex conditions. Here, we investigate progress across the melanoma treatment landscape, with a look at recent remarkable therapeutic advances as well as investigational agents in the pharmaceutical pipeline. Our authors also discuss breakthroughs in the management of pulmonary arterial hypertension (PAH), highlighting results of clinical trials that shed light on the role of combination therapies in treating PAH. In addition, we explore the clinical benefits of new-to-market treatments in the management of irritable bowel syndrome (IBS). We also discuss the clinically appropriate use of Long Acting Reversible Contraceptives (LARCs), trends in utilization, and implications for managed care decision makers. We conclude the publication with a feature that highlights the management and treatment of human immunodeficiency virus (HIV) and explores innovative management strategies for payers.

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

Sincerely,

Maria Lopes
Chief Medical Officer
Magellan Rx Management

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Managed Care Newsstand

Study: Priority Health Wellness Plan Reduces Costs, Improves Care

Priority Health's hybrid health plan that features wellness incentives has reduced employer costs and improved employee health, according to the results of a five-year study. Priority Health launched **Health**byChoice® plans in 2007 to reward participants who get and remain healthy. These incentive-based plans use five indicators — tobacco use, body mass index, blood pressure, cholesterol, and blood sugar — to measure employee health. The plans raise awareness of these potential health risks and reward members who make measurable progress that improves their health.

The study looked at the effect of the **Health**byChoice plans on cost and chronic conditions. They compared nine employer groups with **Health**byChoice plans to nine groups without the plans. The plans included about 9,000 members.

In terms of cost, members in the **Health**byChoice plans saved employers 12 percent in claims costs or an average of $60 per member per month. The total cost savings over four years was about $1.2 million.

The study found that participants in the **Health**byChoice plans showed a reduction in the development of chronic diseases. The researchers reported that **Health**byChoice plans members were 27 percent less likely to develop chronic lung disease, 26 percent less likely to develop diabetes, and 26 percent less likely to develop ischemic heart disease.

"Employers are taking a greater interest in the well-being of their employees, and for good reason," said Marti Lolli, Priority Health senior vice president of commercial products. "Healthier employees mean lower cost and less absenteeism. The **Health**byChoice plans are creating the return on investment employers are looking for in their workplace wellness programs."

Priority Health is adding online support tools to enhance its **Health**byChoice plan. These tools will help members who want to quit smoking, track their activity and nutrition, and manage stress.

Source: A Priority Health wellness plan is proven to lower employer costs and improve employee health. Priority Health. News release. May 16, 2016.

Horizon Blue Cross Blue Shield of New Jersey and Trinitas Regional Medical Center Join Forces in Value-Based Care Collaborative

Horizon Blue Cross Blue Shield New Jersey (Horizon BCBSNJ) and Trinitas Regional Medical Center are launching a new partnership to improve the health and well-being of residents of Elizabeth, NJ, and surrounding communities. This collaboration will integrate Horizon's patient-centric, value-based care models at Trinitas in an effort to increase the quality and access of care and reduce health care costs.

This year, the collaboration's initial focus will be on patients with congestive heart failure and will incorporate Horizon's innovative "Episodes of Care for Heart Failure" protocols into Trinitas' cardiac care program. The Episodes of Care program will expand in 2017 to include "Episodes of Care for Coronary Artery Disease" and "Episodes of Care for Diabetes," which will also be integrated at Trinitas.

Horizon and Trinitas will also work together to develop a program that will enhance the quality of care and reduce costs for those on Medicaid. They plan to establish a care model that integrates primary care and behavioral health services for patients with medical needs, as well as mental or substance abuse conditions.

"Horizon is committed to working with urban hospitals that want to collaborate with us to do even more to improve care quality, enhance the patient experience, and control health care costs," said Robert A. Marino, chairman and CEO of Horizon BCBSNJ. Marino added, "Through this strategic collaboration, we'll help Trinitas Medical Center accelerate their transition to value-based care by providing incentives for them to coordinate and deliver the full array of treatments and services needed to keep people healthy and get them on the road to recovery more quickly when they become sick."

"This strategic collaborative represents an aggressive strategy to increase access to primary care, better integrate primary and behavioral health services, and deliver care more effectively and efficiently to the people we serve," said Gary S. Horan, FACHE, president and CEO of Trinitas Regional Medical Center. "Value-based care is clearly the direction in which medicine is heading, and we're excited to join Horizon at the forefront of bringing the benefits of this approach to our patients."

Horizon physicians, nurses and team leaders work with their counterparts at Trinitas to improve outcomes and enhance cardiac patients' care from diagnosis through intervention and rehabilitation.

Horizon's Value-Based Care programs — including Episodes of Care, Accountable Care Organizations and Patient-Centered Medical Homes — have a proven track record of enhancing outcomes and patient experience, and reducing costs. As part of the Patient-Centered Medical Homes program, 6,500 participating physicians provide care to more than 800,000 members. Patients in one of these programs have seen significant improvements in several key areas. They have 6 percent higher rates of diabetes control and 7 percent higher rates of cholesterol management, and 8 percent lower rates of hospital admissions and 5 percent lower rates of emergency room visits. They also saw a 9 percent reduction in the total health care costs.

Source: Trinitas Regional Medical Center and Horizon Blue Cross Blue Shield of New Jersey enter into multifaceted value-based care collaborative. Horizon Blue Cross Blue Shield of New Jersey. News release. June 6, 2016.

Oncology Care Model Underway

The U.S. Department of Health and Human Services (HHS) launched a new five-year Oncology Care Model, beginning on July 1, 2016, and running through June 30, 2021, which is designed to foster higher quality, lower cost, and more coordinated cancer care. HHS selected 200 physician groups and 17 health insurance companies to participate in the program, which is one of the first Centers for Medicare & Medicaid Services (CMS) physician-led specialty care models.

Beneficiaries in the Oncology Care Model receive enhanced, timely, and coordinated services that may include:

- Coordinating appointments with providers within and outside the oncology practice
- Offering access to care around the clock
- Ensuring that providers receive needed data and results from patient tests prior to appointments
- Providing access to additional resources such as support groups, pain management, and participation in clinical trials

"As a leader in value-based care with over 65 percent of our members in these arrangements, we are dedicated to providing patients with access at the right time and place," said Karen Ignagni, president and CEO of EmblemHealth, one of the participating health insurance companies. "We are guided by the need to put the patient at the center of care and this initiative further elevates this commitment."

Sources: HHS announces physician groups selected for an initiative promoting better cancer care. US Department of Health and Human Services. News release. June 29, 2016.

CMS announces EmblemHealth selected for initiative promoting better cancer care. EmblemHealth. News release. June 29, 2016.

Cancer Data Initiative Launched to Rapidly Improve Cancer Care

The American Society of Clinical Oncology (ASCO) has launched CancerLinQ™, the nation's largest leading cancer informatics program, to help providers improve care to cancer patients.

Fifty-eight practices in 39 states and Washington, D.C., have joined CancerLinQ. The practices range from small private practices to some of the leading cancer centers in the United States. CancerLinQ gathers real-time data from cancer patients through their electronic health records. In turn, CancerLinQ will allow providers to analyze millions of cancer patient medical records, discover patterns and trends, and compare their care against that of their peers and recommended guidelines.

"CancerLinQ is beginning to fulfill its mission of empowering the oncology community to improve quality of care and patient outcomes," said Kevin Fitzpatrick, CEO of CancerLinQ. "In a fast-changing oncology landscape, doctors are demanding this kind of collaboration and support so they can easily stay on top of new evidence and new treatment approaches, and deliver exactly the care their patients need."

According to ASCO, the CancerLinQ platform is the only program of its type being driven by a non-profit, physician organization. The platform benefits from the combined expertise of ASCO's membership of 40,000 of the world's top oncologists.

Sources: ASCO's CancerLinQ™ extends its reach — 58 oncology practices, 750,000 patient records, 1,000 providers under contract, new partnership launch with the nation's leading cancer informatics association. American Society of Clinical Oncology. News release. June 5, 2016.

Health Plan's Program Helps Reduce Opioid Abuse

Blue Shield of California's three-year Narcotic Safety Initiative saw major results in its first year. The program was launched in 2015 to help plan participants avoid opioid abuse and addiction.

The program aims to reduce inappropriate prescribing and overuse of opioid narcotics by at least half over a three-year period. During the first year, the program achieved:

- An 11 percent decrease in members using the highest doses of opioids
- A 5 percent drop in members using moderately high doses
- A 25 percent reduction in the proportion of new opioid utilizers progressing to chronic use
- An overall drop in all opioid consumption

"The focus of Blue Shield's program is twofold. We want to reduce unnecessary initial use of opioids for acute and chronic pain so that members are not unnecessarily exposed to the potential for chronic opioid dependence or addiction, and also promote safer opioid doses for those already on chronic opioid therapy," said Marcus Thygeson, MD, MPH, Blue Shield of California's chief health officer. "The opioid epidemic in the United States is a serious public health crisis, and we've made it a priority to work together with the rest of the health care delivery system to reduce opioid overuse."

"Health plans can help our communities — providers, patients and policymakers — return to a more rational level of opioid prescribing, while ensuring patients get the care they need," said Kelly Pfeifer, director of high-value care for the California Health Care Foundation.

Source: Blue Shield of California's narcotic safety initiative helps plan participants avoid opioid dependence. Blue Shield of California. News release. June 29, 2016.

The Value of Long-Acting Reversible Contraceptives in Preventing Unintended Pregnancies

Moses Allen, PharmD, MS, MBA, Director, Pharmacy Services, Magellan Complete Care

The unintended pregnancy rate in the United States (US), which has hovered around 50 percent for the past decade, is reported to be at an all-time low since the 1980s, when rates were closer to 60 percent.[1] This reduction can be attributed, in part, to the introduction and use of more reliable contraceptive methods beginning in the mid-1990s; however, despite the wide range of available contraceptive methods (see Table 1), the rate of unintended pregnancies remains elevated, likely due to improper and/or inconsistent use of contraceptives.[1] With perfect use, most contraceptives can substantially reduce the risk of unintended pregnancy, but with typical use, most contraceptives result in high rates of pregnancy (see Table 1). Research has demonstrated that one-third of women at risk for pregnancy who are prescribed contraceptives use them inconsistently or incorrectly, if at all, and account for 95 percent of unintended pregnancies.[2]

Moses Allen
PharmD, MS, MBA

While barrier methods and prescription contraceptives (e.g., oral, topical patch, intravaginal ring) require correct and consistent use in order to prevent pregnancy, the effectiveness of long-acting reversible contraceptives (LARCs — intrauterine devices [IUDs] and subdermal implants) does not depend on patient adherence and their use is associated with a failure rate similar to that of sterilization.[3] The primary reason for the low failure rate associated with LARCs is because there is no requirement for user effort (i.e., patient adherence) from the time of insertion until the time of removal.

Among U.S. women between the ages of 15 and 44 using some method of contraception, the percentage who report using a LARC has steadily increased, rising from 2.4 percent in 2002 to 11.6 percent in 2012.[2,4] Although the percentage of LARC users is increasing, a number of barriers are preventing access to treatment, including misconceptions about the use of LARCs as well as financial constraints, still remain. Given the high health care costs attributed to labor and delivery, payors have begun to increase their efforts in reducing the unintended pregnancy rates among their patient populations, particularly by exploring the development and implementation of clinical programs that encourage the use of LARCs when clinically appropriate.

Costs Attributed to Unintended Pregnancies

In 2010, 51 percent of all U.S. births were paid for by public insurance through Medicaid, the Children's Health Insurance Program, and the Indian Health Service, with an average cost of a publicly funded birth of $12,770, including prenatal care, labor and delivery, postpartum care, and 12 months of infant care.[5] Furthermore, in that same year, the government spent $21 billion on births, abortions, and miscarriages due to unintended pregnancies.[5] Among the 2.8 million unintended pregnancies in the United States in 2011, 42 percent (1.2 million) ended in abortion.[6] Research has proposed that avoiding unintended pregnancies has the potential to save the health care system $15.5 billion.[5] The large health care expenditures and potential for cost savings have caught the attention of payors and led to the desire for the development of payor interventions to address this public health care concern.

LARC Treatment Landscape

While some authors suggest that the LARC class includes synthetic progesterone injections administered every three months, this article will follow the common practice of the Food and Drug Administration (FDA) of regarding only IUDs and subdermal implants as LARCs. The five LARCs available in the United States include four IUDs (Liletta™, Mirena®, ParaGard®, and Skyla®) and one subdermal implant (Nexplanon®) (see Table 2). Copper is the active ingredient in ParaGard, which is believed to prevent conception by interfering with sperm transport and fertilization and perhaps preventing implantation. The other IUDs employ levonorgestrel, a synthetic hormone thought to provide contraception by thickening the cervical mucus, which inhibits sperm passage through the cervix, thereby precluding fertilization; inhibiting sperm mobility and function; and altering the endometrium. The active ingredient in the subdermal implant is another synthetic hormone, etonogestrel, which is thought to prevent conception by suppressing ovulation, increasing the thickness of cervical mucus, and altering the endometrium.

Liletta – The newest addition to the LARC treatment landscape, Liletta, received FDA approval in 2015.[7] Liletta is approved for the prevention of pregnancy for up to three years. Of note, an ongoing clinical trial, with an anticipated completion date of December 2020, is evaluating the safety and efficacy of Liletta for the prevention of pregnancy for up to seven years. Unlike some of the available LARCs, Liletta is not indicated for emergency contraception and is contraindicated in this setting.[7]

Skyla – Skyla, the second most recent addition to the LARC landscape, received FDA approval in 2013 for the prevention of pregnancy for up to three years.[8] This approval marked the first new IUD to enter the marketplace in 12 years.[8,9] Skyla, similar to Liletta, is contraindicated for use as an emergency contraceptive.[8]

Mirena – In 2000, Mirena was approved by the FDA for the prevention of pregnancy for up to five years. At that time, the prescribing information noted that Mirena is recommended for use in women who have had at least one child; however, more recent evidence shows IUDs are safe and effective for nulliparous women.[9-11] Mirena later received FDA approval in 2009 for the treatment of heavy menstrual bleeding in women who also desire a contraceptive.[9] Mirena is also contraindicated for use as an emergency contraceptive.[9]

ParaGard – ParaGard T380A, unlike the aforementioned agents, is indicated for the prevention of pregnancy for up to 10 years.[12] Furthermore, ParaGard can also be used as an emergency contraceptive, provided it is inserted within five days after the first act of unprotected sexual intercourse or no longer than five days after ovulation, if the date of ovulation can be estimated.[12,13] The rationale for the specific time frame for insertion is to ensure that the copper IUD acts as a contraceptive rather than as an abortifacient.[14]

Nexplanon – Of the five LARCs available in the United States, Nexplanon is the only subdermal implant available and is indicated for the prevention of pregnancy for up to three years.[15] Nexplanon was preceded by the non-radiopaque etonogestrel implant, Implanon®, which is no longer available. Compared to its predecessor, Nexplanon offers a simpler insertion method with more precise subdermal placement.

Current Guidelines

Due to their high levels of effectiveness and safety among the majority of patients, the American College of Obstetricians and Gynecologists (ACOG) recommends LARC methods as

first-line contraception for most women and adolescents.[16] Specifically, LARCs offer the most effective form of reversible contraception, with an associated rate of pregnancy mirroring that of sterilization: less than 1 percent annually with typical use.[17] The use of LARCs is also accompanied by potential health risks, including uterine expulsion, uterine perforation, pelvic inflammatory disease (PID), and if pregnancy occurs while an IUD or implant is in place, ectopic pregnancy may result.[17]

Barriers to LARC Utilization

Several barriers to LARC utilization have been identified (see Figure 1), with the primary barriers discussed below.

Financial Concerns: Implementation of the Patient Protection and Affordable Care Act (ACA) has made LARCs more affordable for women who have commercial health insurance.[18] Between 2010 and 2013, the proportion of claims for IUDs and implants involving no cost-sharing rose dramatically.[19] However, low-income women in states that have not expanded their Medicaid programs and women who work for employers that cite a religious exemption have not benefited from the ACA as it pertains to LARC affordability. Further, because the ACA mandate does not require that health insurance plans cover every prescription contraceptive available, out-of-pocket expenses have not entirely disappeared. In 2012, 58 percent of women with private health insurance would have faced out-of-pocket costs for IUDs, yet in 2014, only 13 percent still had out-of-pocket costs for IUDs.[20] Because of the ACA, the mean out-of-pocket cost for LARCs has declined steeply, from $262 and $320 in 2012 for an IUD or implant, respectively, to $84 and $91, respectively, in 2013.[21]

Lack of Information Provided to Patients: Recent studies suggest there is a general lack of knowledge about the risks, benefits, and effectiveness of the various contraceptives available, and many myths and misperceptions about LARCs. One survey revealed that a large percentage of women are unaware that an IUD cannot cause an abortion if a woman becomes pregnant while using one, IUDs do not cause infertility, and IUDs are more effective than oral contraceptives at preventing pregnancy.[22] The respondents also cited their lack of sufficient knowledge to feel comfortable with LARCs as the main reason that would prevent them from using LARCs.[22]

One study, the Contraceptive CHOICE Project in St. Louis, included participants from public health clinics serving women at high risk of unintended pregnancies and sexually transmitted infections.[23] After comprehensive counseling about the effectiveness, risks, and benefits of all reversible contraceptive methods, the women used the information to choose a contraceptive method.[23] Prior to the counseling, the participants listened to a short script about contraceptive effectiveness and then completed a questionnaire assessing their knowledge of the effectiveness of various contraceptives. The results of the questionnaire demonstrated that among the 71 percent of women who chose IUDs or implants after comprehensive counseling (and after contraceptives were offered at no cost), these individuals were seven times more likely to have previously known the

Table 1. Effectiveness of Birth Control Methods and Rate of Use in the United States[2,28]

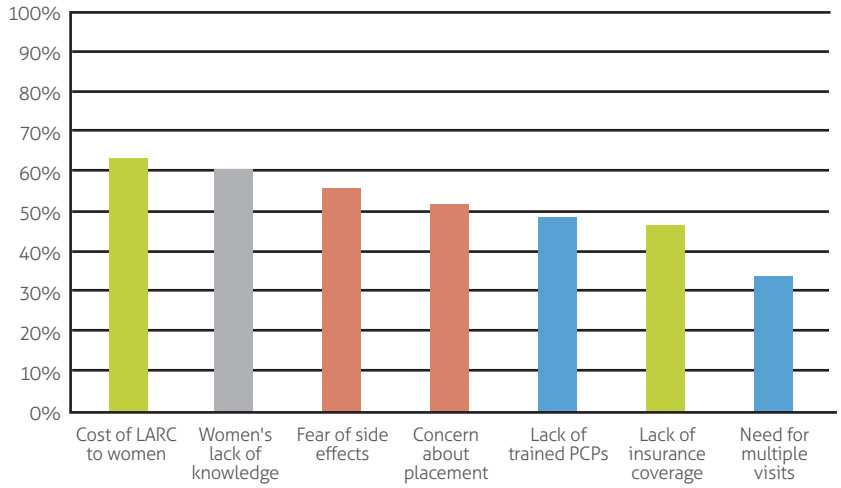
Method	Pregnancy Rate, First Year*	% of Contraceptive Users Who Use Method**	Woman's Actions Required to Use Method
Subdermal Implant	0.05%	1.3%	None, except to replace after 3 years, if desired
Intrauterine Device	0.2-0.8%	10.3%	None, except to replace after 3, 5, or 10 years, if desired
Sterilization	0.15-0.5%	25.1% (female), 8.2% (male)	Elect procedure or encourage male partner to do so
Injection	6%	4.5%	Receive injection every 3 months
Oral Contraceptive	9%	25.9%	Take every day
Transdermal Patch	9%	0.6%	Change every week
Vaginal Ring	9%	2.0%	Change every month
Diaphragm	12%	<0.4%	Use during each instance of intercourse
Condom, Male	18%	15.3%	Use during each instance of intercourse
Condom, Female	21%	<0.4%	Use during each instance of intercourse
Withdrawal	22%	4.8%	Rely on partner to withdraw prior to ejaculation
Cervical Cap	17-23%	<0.4%	Use during each instance of intercourse
Sponge	12-24%	<0.4%	Use during each instance of intercourse
Rhythm Method (fertility awareness)	24%	1.4%	Complete training; periodically practice abstinence or use barrier method
Spermicide	28%	<0.4%	Use during each instance of intercourse
No Method	85%		

**Percentage of women who become pregnant during first year of typical use*
***Percentage of contraceptive users reporting use of this method in the past month (2012)*

Figure 1. Expert Opinion: Barriers to LARC Utilization[32]

There are seven leading reasons that prevent women in the United States from using LARCs, according to a survey of 104 researchers who have published articles about LARCs. Two of the leading barriers are financial (green), two involve patient worries (pink), and two involve provider issues (blue).

Lack of knowledge (2nd bar) extends to women's lack of knowledge about the safety and acceptability of LARCs. Women's lack of knowledge of LARC efficacy ranked eighth (not shown in figure) on the experts' list of barriers, cited by 29% of respondents. Other barriers were related to business issues (challenges stocking LARC, cited by 25%; providers' reimbursement, 19%; billing, 19%), lack of trained family planning providers (15%), women's concerns about LARC removal (14%), and unnecessary screening tests (5%).



true effectiveness of their chosen methods than the women who chose the pill, patch, or ring.[23] However, the 29 percent of CHOICE participants who selected non-LARC contraceptive methods did so after receiving the same information about contraceptive effectiveness, suggesting that factors other than effectiveness are given high priority by some women when they choose a contraceptive method.[23]

It was also observed that participants who selected LARCs were more likely to continue with this method than the women who selected non-LARCs. After 12 months, the continuation rate among LARC users was 87 percent compared to 57 percent for the participants who selected non-LARCs.[24] After 24 months, the continuation rate among LARC users was 77 percent (higher than the rate after 12 months for any non-LARC method), compared to only 41 percent among non-LARC users. This may suggest that although non-LARC users initially selected their contraceptive methods for a reason other than effectiveness, the initial rationale may have been insufficient for most of them to continue using that method in the long-term setting.

Same-Day Insertion: Many patients who request LARCs are instructed to return for another visit for insertion; however, a large percentage of these individuals fail to schedule the second appointment with either the initial provider or a referral. In a survey of ACOG fellows, nearly all the responding obstetrician-gynecologists said they provide IUDs, with 77 percent reporting that they required two visits and 9 percent requiring three or more visits.[25] Only a small proportion of respondents reported offering IUD insertion immediately after birth (7 percent), or abortion or miscarriage (12 percent).

Family medicine physicians have been much less likely than obstetrician-gynecologists to recommend IUDs, let alone insert them.[26] Although current residents in family medicine report being well-informed about the risks and benefits of IUDs and a high percentage note they intend to provide IUDs in their practices, misperceptions continue, as demonstrated by their beliefs that women are inappropriate candidates for an IUD if they have a history of PID or ectopic pregnancy, or no pap smear in the past year and are not in a monogamous relationship, none of which are true contraindications for use.[26]

Pain from IUD Placement: To minimize discomfort associated with IUD insertion, ACOG suggests the use of an over-the-counter pain-relief medication prior to the procedure;[17] however, studies involving various pain medications (e.g., NSAIDs, misoprostol, local anesthetics) have shown they offer little benefit in the relief of insertion-associated pain.[27]

Payors' Strategies: Clinical Programs Encouraging Appropriate LARC Use

Although the ACA eliminated cost-sharing for many users of LARC, a drastic increase in LARC utilization was not observed during the first year of implementation of the mandate that required most private insurers to provide contraceptive services without cost-sharing.[19] To encourage the use of LARCs when clinically appropriate and reduce the rate of unintended pregnancies, payors should encourage providers to follow the LARC best practices, as published by the ACOG, Centers for Disease Control and Prevention (CDC), and World Health Organization (WHO):[13,28]

1. If pregnancy can reasonably be ruled out, provide LARC the same day a woman requests it, whenever possible.
2. Offer LARC at the time of delivery, abortion, or dilation and curettage for miscarriage.
3. Provide screenings for sexually transmitted diseases (STDs) at the time of LARC insertion. If the screening test result is positive, treat the infection without removing the LARC.
4. For emergency contraception, offer the copper IUD due to its improved effectiveness over other available emergency contraceptives.[14] Further, once a copper IUD has been inserted as an emergency contraceptive, it remains in place as an ongoing long-term contraceptive.

The CDC has suggested that payors can encourage the appropriate use of LARCs by employing a variety

Table 2. FDA-Approved Long-Acting Reversible Contraceptives Available in the United States[7-9,12,15]

Brand Name / Manufacturer (Generic Name)	FDA Approval	Approved Life Span	Product Description	Wholesale Acquisition Cost/WAC**
Intrauterine Devices (IUDs)				
ParaGard T380A / Teva (intrauterine copper contraceptive)	11/15/1984	10 years	T-shaped IUD has 176mg of copper wire coiled along 36mm stem of and 68.7mg copper collar on each arm; exposed copper surface of 380mm^2 continuously releases copper into uterine cavity Barium sulfate in 32x36mm T-frame facilitates X-ray detection	$739.00 per device
Mirena* / Bayer (levonorgestrel-releasing intrauterine system)	12/6/2000	5 years	Reservoir containing 52mg of levonorgestrel releases hormone at initial rate of about 20mcg/day, progressively falling to half that value after 5 years Barium sulfate in 32x32mm T-frame confers radiopacity	$858.33 per device
Skyla / Bayer (levonorgestrel-releasing intrauterine system)	1/9/2013	3 years	Reservoir containing 13.5mg of levonorgestrel releases hormone at rate of about 14 mcg/day after 24 days, 10mcg/day after 60 days, and 5mcg/day after 3 years Barium sulfate in 28x32mm T-frame makes IUD radiopaque	$714.70 per device
Liletta / Actavis Pharma (Allergan); Medicines360 (levonorgestrel-releasing intrauterine system)	2/26/2015	3 years	Reservoir containing 52mg of levonorgestrel releases hormone at initial rate of 18.6mcg/day, about 16.3mcg/day by end of year 1, 14.3mcg/day by end of year 2, and 12.6mcg/day by end of year 3 Barium sulfate in 32x32mm T-frame makes IUD radiopaque	$625.00 per device
Subdermal Implant				
Nexplanon Radiopaque / Merck (etonogestrel implant)	7/17/2006	3 years	Reservoir containing 68mg of etonogestrel releases hormone at initial rate of 60-70mcg/day in week 5-6 after implant, falling to 35-45mcg/day at end of year 1, 30-40mcg/day at end of year 2, and 25-30mcg/day at end of year 3 Barium sulfate confers radiopacity to 4cmx2mm implant, a characteristic lacking in its discontinued predecessor, Implanon Shipped with preloaded insert to facilitate correct subdermal placement	$771.52 per device

**Also indicated for treatment of heavy menstrual bleeding for women who elect IUD for contraception*
***Micromedex. Red Book Online. 2016*

of interventions. One such example of an intervention is adjusting the reimbursement strategy to include reimbursement for the full range of contraceptive services, including screening for pregnancy intention, tiered contraception counseling, and the insertion, removal, replacement, or reinsertion of LARCs, along with follow-up.[5] This adjusted reimbursement model, as recommended by the CDC, should focus on providing reimbursement for the actual cost of the LARC, and consideration should be given to providing additional reimbursement for the cost of services associated with the insertion or placement of the device or implant.[5] The CDC has acknowledged the high up-front costs associated with LARCs, but suggests that these methods remain cost-effective options over the course of their use, even if the methods are not used for their full duration of efficacy, compared to their short-acting counterparts.[5]

A second recommended payor intervention is the unbundling of the payment for LARC from other postpartum services and reimbursing immediate LARC insertion in the postpartum setting.[5] The CDC suggests that current reimbursement strategies offer a disincentive to providers to offer LARC in the postpartum setting, as they are not reimbursed separately from the single bundled payments for labor and delivery if the LARC insertion or placement procedure is performed while

the woman remains in the hospital after delivery.[5] It has been reported that the unbundling of LARC payments has resulted in a decrease in the rates of rapid, repeat pregnancies among the states that have implemented this reimbursement method.[29] Further research has demonstrated that over a period of two years, immediate postpartum LARC placement avoided 88 unintended pregnancies per 1,000 women, resulting in a savings of $282,540 for every 1,000 women, and a savings of $3,200 for each unintended pregnancy.[30]

The third proposed payor intervention is the removal of administrative and logistical barriers to LARC.[5] The CDC suggests that payors can update their policies to reflect the elimination of prior authorizations for LARC, and not require multiple provider visits or previous contraceptive failure as a qualification for LARC coverage.[5] Other suggestions include enhancing providers' knowledge through continuing education programs that increase awareness about the ACOG guidelines, recommending LARC in the first-line setting, and implementing a direct payment arrangement between payors and pharmacies to assist with providers' access to LARCs without absorbing large acquisition costs.[5]

As payors strive to increase the use of LARCs, it is imperative that the emphasis remain on health care providers presenting women with all pertinent information required to make fully informed choices. Such information should include, but not be limited to, the very low failure rates associated with LARCs, the continued need for the use of barrier methods to reduce the risk of sexually transmitted infections (STIs), the risks associated with LARC use, as well as a comprehensive overview of the benefits of oral contraceptives compared to LARCs (e.g., acne treatment, no requirement for office visit for treatment discontinuation). Payors should also encourage primary care providers to enhance their knowledgeability of and skill in placing IUDs and implants so they are able to provide LARCs for women who select this method of contraception, preferably on the day it is requested by the patient.[31]

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Take a closer look at NINLARO® (ixazomib) to see how it improved median progression-free survival (PFS) when added to lenalidomide and dexamethasone.

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia** has been reported with NINLARO. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines. Adjust dosing as needed. Platelet nadirs occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle.
- **Gastrointestinal Toxicities**, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.
- **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.
- **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.
- **Cutaneous Reactions:** Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification.

NINLARO®
(ixazomib) capsules
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Consider another option for your members.

The first and only oral proteasome inhibitor (PI), the NINLARO regimen delivers approximately 6 months of improved PFS to your members with multiple myeloma who have received at least one prior therapy.* In the first clinical trial using an all-oral, PI-based treatment to progression or unacceptable toxicity, the NINLARO regimen provided 20.6 months of median PFS compared to 14.7 months with the placebo regimen.[1]*

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

TO SEE WHAT'S POSSIBLE WITH NINLARO, VISIT WWW.NINLARO-HCP.COM/TAKEALOOK

*NINLARO regimen=NINLARO+lenalidomide+dexamethasone; placebo regimen=placebo+lenalidomide+dexamethasone

- **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.
- **Embryo-fetal Toxicity:** NINLARO can cause fetal harm. Women should be advised of the potential risk to a fetus, to avoid becoming pregnant, and to use contraception during treatment and for an additional 90 days after the final dose of NINLARO.

ADVERSE REACTIONS

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

SPECIAL POPULATIONS

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

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

TOURMALINE-MM1: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of NINLARO (an oral PI) vs placebo, both in combination with lenalidomide and dexamethasone, until disease progression or unacceptable toxicity in 722 patients with relapsed/refractory multiple myeloma who received at least 1 prior therapy.[2]

CI=confidence interval; NE=not evaluable; HR=hazard ratio.

References: 1. Data on File 101, Takeda Pharmaceuticals International Co. **2.** Data on File 102, Takeda Pharmaceuticals International Co.

Please see Brief Summary for NINLARO adjacent to this advertisement.

Takeda ONCOLOGY

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

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

1 INDICATION

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 CLINICAL TRIALS EXPERIENCE

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

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

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

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

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

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

*Represents a pooling of preferred terms

(Continued on next page)

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

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

Eye Disorders

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

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

8.5 Geriatric Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

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

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

17 PATIENT COUNSELING INFORMATION

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

Dosing Instructions

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

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

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

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

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

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

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

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

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

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

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

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Combination Therapy in Pulmonary Arterial Hypertension (PAH): What We Know and What We Do Not Know

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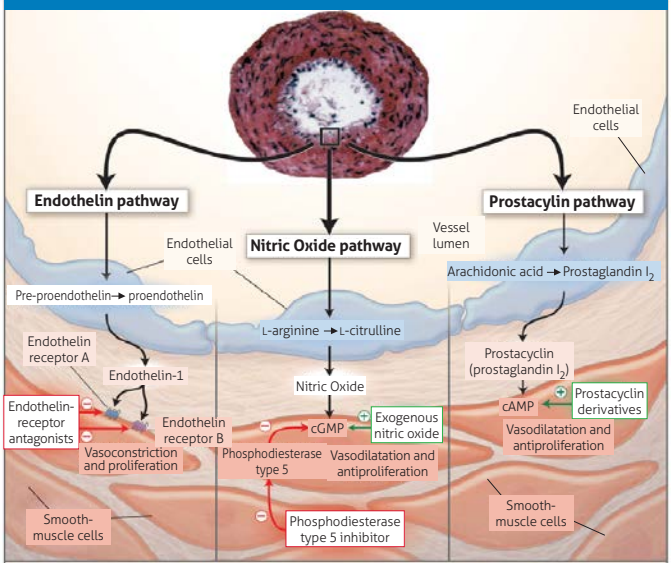
Pulmonary arterial hypertension (PAH) is a rare subtype of pulmonary hypertension characterized by proliferative vasculopathy of the small pulmonary arteries leading to increased pulmonary vascular resistance (PVR) and ultimately to right ventricular failure and death.[1] Endothelial dysfunction in the pulmonary vascular bed is thought to trigger development of PAH. Increased levels of plasma endothelin, along with lower levels of nitric oxide and prostacyclin, are implicated in PAH pathogenesis.[2] Currently there are three targeted pathways with five approved classes of drugs to treat PAH — endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanlyate cyclase stimulators, prostacyclin analogues and prostacyclin receptor agonists. The potential interaction between these three pathways may improve treatment outcomes, as seen in other disease states, such as hypertension, diabetes and oncology.[3] (See Figure 1.) Combination therapy that targets the different PAH pathways is an attractive therapeutic option.[2]

Figure 1. Targets for Current or Emerging Therapies in PAH[27]



PAH is a rare disease with an annual U.S. incidence of 2.3 and prevalence of 12.4 cases per million.[4] Recent estimates from the REVEAL Registry (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) indicate a median survival of >7 years following diagnosis for patients receiving specific PAH treatment and a one-year incident mortality rate of 15 percent.[5]

Patients have been treated with PAH-specific drugs since epoprostenol (Flolan) was approved in 1995. For many years, monotherapy was the standard of care, although physicians used sequential combination therapy, ahead of trial evidence, when patients failed to achieve satisfactory results. In the early 2000s, the Hanover algorithm proposed sequential combination therapy (bosentan, add sildenafil, add inhaled iloprost, and transition to IV iloprost) when treatment goals were not met.[6] Subsequently guidelines, clinical trials and expert algorithms provided support for combination therapy. While combination therapy has arguably become the new standard of care,[7] gaps in knowledge of combination therapy remain. It is unclear whether initial or sequential combination therapy is better. This article is directed to managed care audiences, those making formulary decisions to optimize care of patient populations while managing health care resources, and will describe what is and what is still not known about combination therapy in PAH.

Clinical Trial Evidence

The first trial using initial combination therapy, BREATHE-2 (2003), assessed the safety and efficacy of bosentan in combination with epoprostenol in 33 WHO Functional Class (FC) III and IV patients.[8] Although the trial was not positive, there was a trend toward improvement in hemodynamic parameters. Three bosentan deaths were reported, reflecting the severity of the disease. The STEP trial was conducted to assess the safety of adding an ERA (bosentan) to a prostacyclin (iloprost); efficacy was the secondary endpoint. In the 12-week trial, there was a numerically greater 6-minute walk distance (6MWD) in the combination versus the bosentan-only group. Safety data was consistent with previous trials, and comparable efficacy (TTCW [time to clinical worsening], FC and hemodynamics) was shown. As newer therapies were approved, several pivotal trials included patients on existing PAH background therapy. In the EARLY trial, bosentan was studied only in FC II patients, with approximately one-fifth of patients on stable doses of sildenafil. At month 6, geometric mean pulmonary vascular resistance (PVR) demonstrated a treatment effect of 22.5 percent ($p<0.0001$); however, the treatment effect on 6MWD was not statistically significant (19.1 m; $p=0.0758$). No individual serious adverse events were reported.[9]

In the PHIRST trial, treatment-naïve or background bosentan plus tadalafil or placebo patients were studied. At week 16 in treatment-naïve patients, tadalafil 40 mg improved placebo-adjusted 6MWD by 44 m ($p<.01$). Commonly reported mild to moderate adverse events were headache, myalgia and flushing, with similar discontinuation rates across all treatment groups.[10]

In TRIUMPH, inhaled treprostinil was studied in patients treated with bosentan (70 percent) or sildenafil (30 percent) or placebo. Overall there was an improvement of approximately 20 m in the 6MWD ($p=.0004$) driven by an increase in 6MWD (25 m; $p<0.0002$) for the bosentan background group. Results for the sildenafil background group were nonsignificant (9 m). The most common side effect was cough, and 11 treprostinil patients experienced a serious adverse event (AE).[11]

PACES was the first study of significant size (n=267) that addressed combination therapy, adding sildenafil 80 mg three times daily (TID) (four times the approved dose) to long-term intravenous (IV) epoprostenol in patients. There was a statistically significant placebo corrected increase in 6MWD (28.8 m; $p=.001$), and improvements were seen in hemodynamic parameters (mPAP and CO), TTCW and quality of life (QoL). Headache and dyspepsia were AEs observed more often in sildenafil-treated patients.[12] More recently (2013), the PATENT-1 trial (n=444) investigated the safety and efficacy of riociguat in both monotherapy and combination therapy. The 12-week trial included 222 patients (194 patients on an ERA and 28 on a nonintravenous prostanoid). Riociguat demonstrated efficacy in monotherapy and combination therapy (improvement in 6MWD, PVR, NTpro-BNP, WHO FC, TTCW, QoL and Borg dyspnea score). The most common AEs were headache, dyspepsia and peripheral edema.[13]

While a number of trials using combination therapy have demonstrated positive results, the FREEDOM-C and FREEDOM-C2 trials did not demonstrate such efficacy. The FREEDOM-C study investigated the effect of adding oral treprostinil to the treatment regimen of 350 patients receiving either ERA and/or PDE5 inhibitors. At 16 weeks, the primary endpoint, improvement in 6MWD, did not reach statistical significance. A number of AEs resulted in discontinuing study drugs, including headache, nausea, diarrhea, vomiting, worsening PH, extremity pain, chest discomfort and myalgia.[14]

Historically, change in 6MWD has been the most frequently used primary endpoint in randomized, controlled trials (RCTs) with PAH patients. Studies suggest, however, that the 6MWD has only modest validity as a surrogate endpoint for clinical events.[15] Supported by expert recommendations, recent pivotal trials for new PAH drugs have moved from short-term trials with a functional endpoint to longer, larger, event-driven trials with a composite morbidity/mortality (M/M) endpoint. In the proceedings of the fifth WSPH, TTCW was advocated as an appropriate endpoint in pivotal trials. The experts proposed a group of clinical endpoints, including all-cause death, lung transplantation, hospitalization for worsening PAH (including atrial septostomy), initiation of IV therapy due to worsening of PAH, worsening of function (measured by worsening FC and exercise capacity) and worsening of PAH symptoms (dyspnea, chest pain, dizziness/syncope and fatigue/activity level).[16]

Several studies using sequential combination therapy in event-driven M/M trials have been done. Although these trials have been largely positive, this is not uniformly true. For example, COMPASS-2, utilizing a composite M/M primary endpoint, evaluated sequential therapy with sildenafil and bosentan.[17] The long-term (median 22.7 months) trial failed to demonstrate positive results for the primary endpoint, as the observed risk reduction of a M/M event for bosentan (added to sildenafil) versus placebo was not statistically significant. No new safety signals occurred.[17]

SERAPHIN was the first placebo-controlled, long-term, event-driven trial for drug registration. In SERAPHIN, macitentan was studied in patients already on PAH-specific therapy (PDE5i or nonparenteral PGI2) and in monotherapy patients using a combined M/M endpoint. There was a statistically significant 45 percent reduction ($p<0.001$) in the risk of the combined endpoint for patients treated with macitentan 10 mg versus placebo patients, which was driven by deterioration in PAH. Macitentan also reduced the risk of the combined endpoint of PAH-related death or hospitalization. Risk reduction was consistent in monotherapy and combination therapy and in both incident and prevalent patients. Adverse events occurring more frequently with macitentan than with placebo included headache, nasopharyngitis and anemia.[18]

In the GRIPHON trial, the novel prostacyclin IP receptor agonist — selexipag — was studied in a long-term, event-driven, placebo-controlled trial using a composite M/M endpoint.[19] At the time of randomization, 80 percent of the patients were on an ERA or a PDE5i while nearly one-third of patients were on both an ERA and a PDE5i. Selexipag

reduced the risk of the composite endpoint by 40 percent (p<0.001), without regard to whether the patient was on monotherapy or combination therapy with two or three PAH-specific agents. The risk reduction was driven by PAH deterioration and a decrease in hospitalization. The most common AEs in the selexipag group were consistent with known prostacyclin side effects (headache, diarrhea, nausea and jaw pain).[19] This trial was unique because this was the first RCT that demonstrated efficacy with triple therapy.

In the AMBITION trial, ambrisentan was studied in initial combination therapy with tadalafil (both drugs were up-titrated over an eight-week period) versus ambrisentan or tadalafil monotherapy. For the primary analysis, both groups were combined as pooled monotherapy. This was a long-term, event-driven trial with clinical failure as the primary endpoint. No placebo group was included in the study. The risk reduction for the primary endpoint in the ambrisentan/tadalafil combination-therapy group versus the pooled-monotherapy group was 50 percent (p<0.001). Adverse events occurring more frequently in the combination-therapy group than in either monotherapy group included peripheral edema, headache, nasal congestion and anemia. This trial was unique in that it was a treatment strategy trial and only incident patients were studied.[20] Results from this trial contributed to inclusion of initial combination therapy in expert guidelines (ESC/ERS 2015) for the first time.

Meta-Analyses

Combination therapy is widely used when PAH patients have a suboptimal response to initial PAH-specific monotherapy. At present, sequential combination therapy is the most widely used clinical practice strategy. While RCTs have shown drug-specific evidence, it is interesting to address the evidence across all PAH-specific drugs through meta-analysis. Recently, Liu et al., performed the first meta-analysis that separately analyzed monotherapy and combination therapy to assess the efficacy and safety of PAH-specific therapy. Databases were searched through October 2015, with 418 records identified; 35 studies met the required criteria and were included in the meta-analysis. Compared to the control group, PAH-specific therapy was associated with significant improvement in mortality (OR: 0.71; p<0.004), as well as statistically significant improvements in FC, 6MWD and hemodynamics. PAH-specific therapy was associated with a higher incidence of withdrawal due to adverse effects (OR: 1.53; p<0.00001). Specifically for combination therapy, data was available from 15 RCTs. Combination therapy did increase 6MWD by 19.96 m (p<0.00001) and improve FC (OR 1.65; p=0.002) and was also associated with statistically significant improvements in hemodynamics, including PVR and mPAP, but was not statistically significant for CI. Combination therapy was associated with a higher incidence of withdrawal due to adverse effects (OR: 2.01; p<0.00001).[21] While combination therapy was positive overall, there was no mortality benefit that may be accounted for by the short follow-up period and small sample size. Lajoie et al., also performed a meta-analysis to assess the effects of a combination of PAH-specific therapies compared with monotherapy on predefined clinical worsening in PAH.[22] Of 2017 studies that were identified (published from January 1990 to May 31, 2015), only 15 studies were included in the primary analysis. Combined therapy was associated with significant risk reduction (RR: 0.65; p<0.00001) for clinical worsening (17 percent - 332 of 1,940 patients) versus monotherapy (28 percent - 517 of 1,862 patients). Findings from sensitivity and subgroup analyses confirmed the result robustness and suggested that the effect of combination therapy on clinical worsening was not driven by any particular drug class, study design or patient/disease characteristics. Combination therapy was not associated with significant reductions in death and transplantation as first events. The authors stated this endpoint may be negatively impacted by the risk of other competing components of a composite endpoint assessed as a time to first event. "Because admissions to hospital, transplantations and deaths most commonly occur subsequent to symptomatic progression or admission to hospital, the use of a time-to-first-event outcome might have underestimated the treatment effect of combination therapy on these subsequent outcomes."[22] Combination therapy, however, was associated with an increased risk for treatment discontinuation.

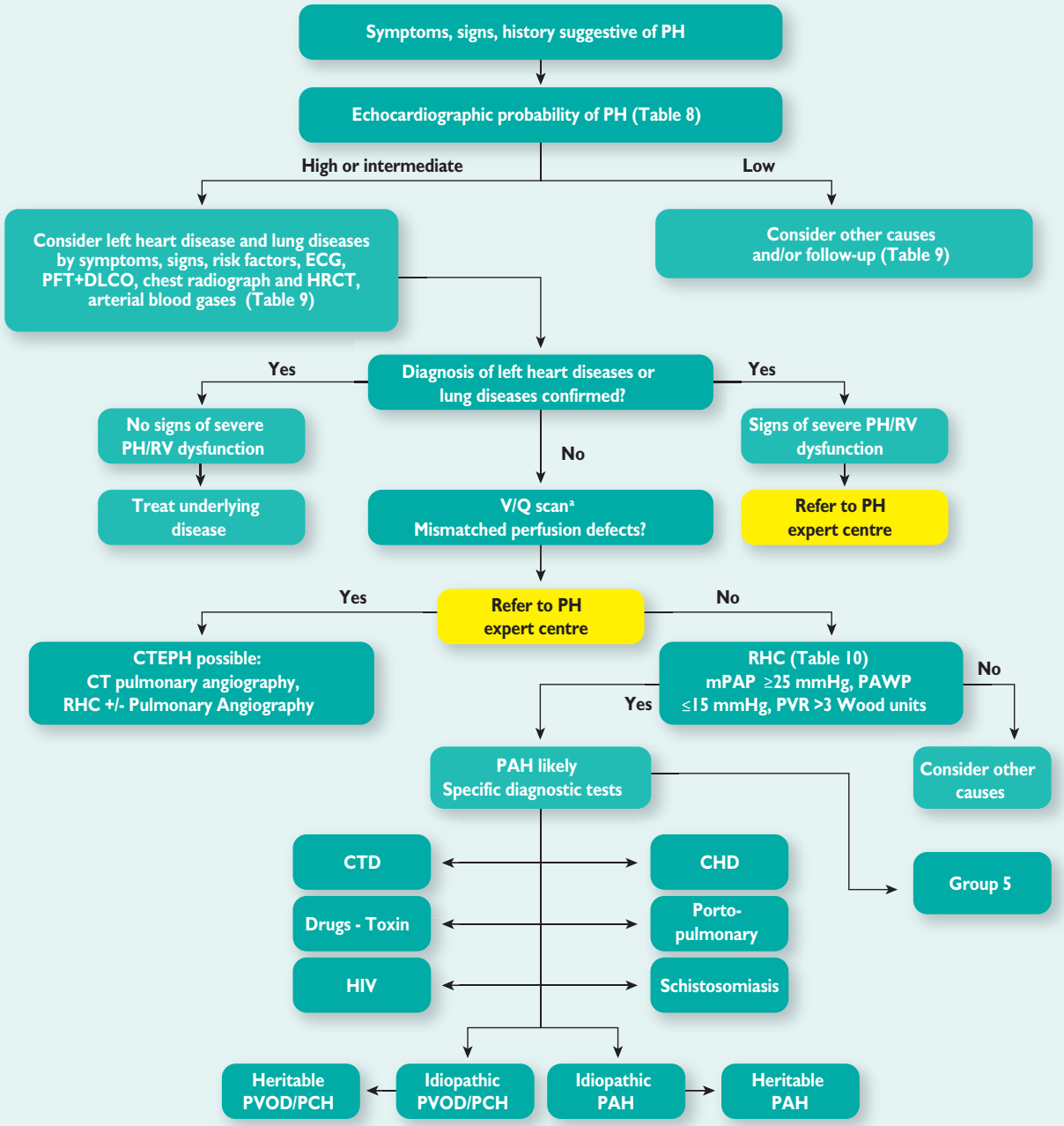
Limitations of these meta-analyses include lack of investigation of cost-effectiveness of the therapies, and these analyses did not separately evaluate the effect of sequential versus initial combination therapy. Therefore, no information was provided on whether sequential combination or initial combination offers a more beneficial outcome.

Expert Guidelines/Algorithms

For more than a decade, experts have included combination therapy within treatment algorithms as a therapeutic consideration. In the Third World Symposium on PH proceedings, held in 2003 in Venice, an algorithm was presented for NYHA FC III or IV patients. (At this time, very little information was available for patients in FC I or II.) Even though data was limited and uncontrolled, the proceedings recommended that combination therapy be considered for patients who do not show improvement or deteriorate with first-line therapy.[23]

By the time the Fourth World Symposium on PH proceedings was held in Dana Point, California, in 2008, a number of clinical trials had been done that included combination therapy. These studies supported the efficacy of combination treatment for those patients still symptomatic on monotherapy. Barst et al., stated that the optimal combination based on the overall risk-benefit considerations remained unknown. However, the algorithm included combination therapy as a consideration when treatment goals were not met on

Figure 2: 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension



CHD = congenital heart diseases; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH = pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capillary hemangiomathosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.

[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

monotherapy.[24] Even though many health care providers had been using combination therapy for a period of time, effectively, the Dana Point algorithm moved combination therapy into mainstream treatment. Now managed care plans that had not previously paid for combination therapy began to "cover" sequential combination therapy for patients who worsened or did not improve on monotherapy. In 2013, when the Fifth World Symposium on PH proceedings was held in Nice, the experts reinforced the place of combination therapy as an option when the patient failed to reach clinical goals on monotherapy.

The most recent (2015) European Society of Cardiology/ European Respiratory Society guidelines provided not only an updated algorithm but also a risk-based assessment strategy to guide therapeutic considerations. Low-risk patients have a one-year mortality risk <5 percent. These patients present with nonprogressive disease (FC I or II) with a 6MWD 440 m and no signs of clinically relevant RV dysfunction. Patients with intermediate mortality risk (5 to 10 percent) are typically in FC III with moderately impaired exercise capacity and signs of RV dysfunction. High-risk patients with mortality risk >10 percent in one year present in FC III or IV with progressive disease, including signs of severe RV dysfunction or failure and secondary organ dysfunction. The main treatment goal is reaching and maintaining a low-risk profile.

For low- or intermediate-risk patients (FC II and III — although some FC III patients may be high risk), the recommendation is for initial monotherapy or combination therapy. For high-risk patients, initial double or triple combination treatment including an intravenous (IV) prostacyclin analogue is recommended. IV prostacyclin use is mandatory for these high-risk patients because it is the only treatment that has shown a survival benefit in patients with severe disease. Recommended for initial combination therapy in incident (newly diagnosed) patients, ambrisentan/tadalafil is the only specific combination studied. For sequential combination therapy, the following drugs are recommended based on clinical evidence: macitentan added to sildenafil; riociguat added to bosentan; and selexipag added to an ERA and/or a PDE5i.

For monotherapy, since no head-to-head comparisons have been done, no evidence-based first-line monotherapy is recommended. Choice of drug depends on physician experience and preference, route of administration, side effect profile, background therapies, patient preferences, comorbidities and cost. Burger et al, in a recent real-world study, revealed 95 percent of PAH patients began with monotherapy.[25] When clinical response to initial combination therapy or initial monotherapy is inadequate, sequential double or triple combination therapy is recommended. Currently, sequential combination therapy is the usual practice.

Discussion

Combination therapy in PAH is an important treatment modality and is the current standard of care for most patients with PAH. With three pathways, targeting two or more of these pathways can provide an additive effect. Both clinical trial evidence and meta-analyses demonstrate benefit on morbidity, functional parameters (6MWD, FC) and hemodynamics with combination therapy. Expert guidelines, both the Nice (2013) and the ESC/ERS (2015), have provided guidance on the place of combination therapy.

However, knowledge gaps remain. For example, how is initial combination therapy defined? Rarely in PAH are two drugs initiated at the same exact time. Is there a "best" combination?

At first glance, AMBITION trial results would lead one to believe that all patients should start with combination therapy, but the evidence is in a specific subset of patients — treatment-naïve patients — and the AMBITION trial is only specific to the ambrisentan/tadalafil combination. Further, edema occurred in almost one of every two ambrisentan/tadalafil patients, which, in clinical practice, necessitates additional clinical evaluation and intervention or discontinuation of one or more of the agents. Many patients who present at an expert center may have been seen by one or more physicians and treated with PAH-specific therapy.[26] The evidence from AMBITION does not provide any data to tell us if initial combination therapy demonstrates superior outcomes for prevalent PAH patients, who make up the bulk of patients in any managed care plan.

Although both the SERAPHIN and GRIPHON trials provide important results for incident and prevalent patients, neither of these trials was designed to reveal which specific combination of therapy works best. In a retrospective analysis of real-world clinical data on newly diagnosed PAH patients from Sitbon et al., looking at ERA (ambrisentan, bosentan) + PDE5i (sildenafil, tadalafil) combination therapies, none of the four ERA-PDE-5i combinations was superior.[2] Tadalafil compared to sildenafil may have performed better in regard to improving hemodynamics, but maximum effective dose, persistency and compliance may have contributed to this difference. Persistency and compliance with combination therapy is another issue that has not been clarified. Two recent meta-analyses (Liu and Lajoie) revealed withdrawal and treatment discontinuation were more likely to occur in patients receiving combination therapy.[21,22]

From a pharmacoeconomic perspective, initial combination therapy is expensive for both patients and managed care organizations. When the AMBITION trial's Kaplan-Meier curves are examined, the biggest step-down occurred at six months for both the combination and the pooled monotherapy arms. This marks the first time that patients could meet the unsatisfactory clinical response component of the composite endpoint. There was no difference between the two groups for this component. Many of these events were hospitalizations, calling into question the cost benefit of up-front combination therapy in the first six months. In long-term, event-driven trials, such as SERAPHIN and GRIPHON, reduction in hospitalizations was beneficial not only in combination but also in monotherapy on macitentan and selexipag, respectively. Lastly, the risk stratification approach from ESC/ERS is an attractive alternative. Using this algorithm, the decision when to use combination therapy is left to the provider and patient. Expert guidelines suggest the patient be reassessed as early as three months, and if goals are not met, adding a second drug at that time. Such patient-tailored therapy may be not only efficacious but also safe and cost-effective. Knowledge gaps on combination therapy still exist. Further research, including real-world studies, is warranted to close these knowledge gaps.

PAH Oral Medications With Pivotal Trials

Study	Drug	Duration	Primary Endpoint	Number of Patients
Study-351[28]	bosentan	12 weeks	6MWD	32
BREATHE-1[28]	bosentan	16 weeks	6MWD	213
EARLY[28]	bosentan	24 weeks	PVR, 6MWD	185
ARIES-1[28]	ambrisentan	12 weeks	6MWD	202
ARIES-2[28]	ambrisentan	12 weeks	6MWD	192
SUPER-1[28]	sildenafil	12 weeks	6MWD	277
PHIRST[28]	tadalafil	16 weeks	6MWD	405
SERAPHIN[28]	macitentan	115 weeks*	Time to first M/M event	742
FREEDOM-M[28]	oral trep	12 weeks	6MWD	228+
GRIPHON[28]	selexipag	71 weeks*	Time to first M/M event	1156
AMBITION[20]	Ambrisentan/tadalafil	73 weeks	First event of clinical failure	500 primary analysis set
Patent-1[13]	Riociguat	12 weeks	6MWD	443

**Median treatment period; +228 = primary analysis group. N = 349; 6MWD=6-minute walk distance; PAH=pulmonary arterial hypertension; PVR=pulmonary vascular resistance.*

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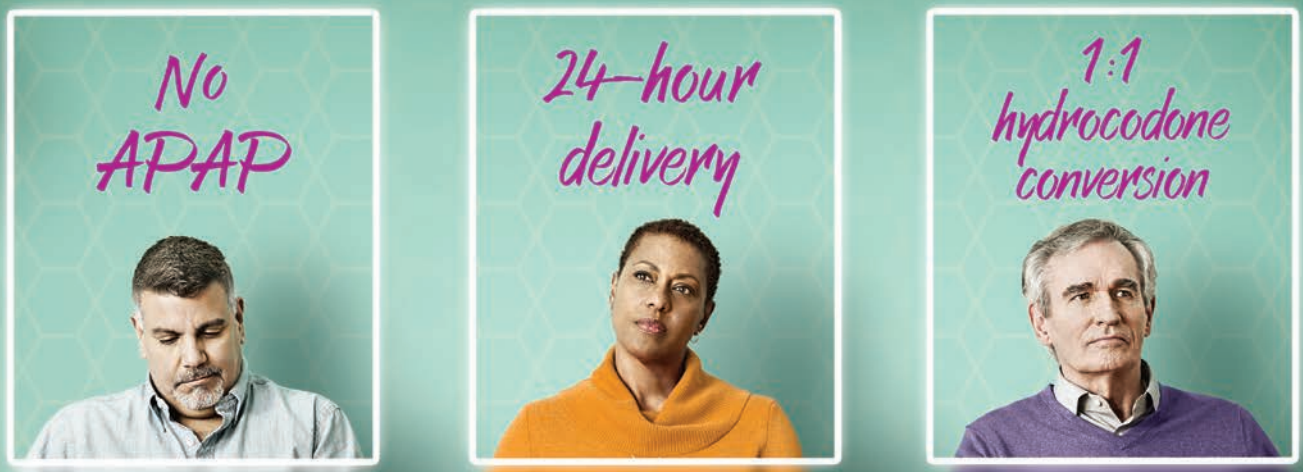

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

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HYSINGLA ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing HYSINGLA ER, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of HYSINGLA ER. Monitor for respiratory depression, especially during initiation of HYSINGLA ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving HYSINGLA ER tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone *[see Warnings and Precautions (5.2)]*.

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  - Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with Hysingla ER
- **The first ER hydrocodone with FDA-approved labeling that describes abuse-deterrent characteristics[2]**
  - The *in vitro* data demonstrate that Hysingla ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the *in vitro* data, also indicate that Hysingla ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed

– However, abuse of Hysingla ER by the intravenous, intranasal, and oral routes is still possible

- With parenteral abuse, the inactive ingredients in Hysingla ER can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury

INDICATIONS AND USAGE

Hysingla® ER (hydrocodone bitartrate) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Hysingla ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Hysingla ER is not indicated as an as-needed analgesic.

CONTRAINDICATIONS

- Hysingla ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected paralytic ileus and gastrointestinal obstruction, hypersensitivity to any component of Hysingla ER or the active ingredient, hydrocodone bitartrate.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

- Hysingla ER contains hydrocodone, a Schedule II controlled substance. Hysingla ER exposes users to the risks of opioid addiction, abuse, and misuse. As extended-release products such as Hysingla ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death, due to the larger amount of hydrocodone present. Addiction can occur at recommended doses and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Hysingla ER, and monitor all patients during therapy for the development of these behaviors or conditions. Abuse or misuse of Hysingla ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death.

For more information, visit HysinglaER.com

See Hydrocodone Differently

Hysingla® ER
(Hydrocodone Bitartrate) II
EXTENDED-RELEASE TABLETS

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with modified-release opioids, even when used as recommended, and if not immediately recognized and treated, may lead to respiratory arrest and death. The risk of respiratory depression is greatest during the initiation of therapy or following a dose increase; therefore, closely monitor patients for respiratory depression. Proper dosing and titration of Hysingla ER are essential. Overestimating the Hysingla ER dose when converting patients from another opioid product can result in fatal overdose with the first dose. Accidental ingestion of even one dose of Hysingla ER, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone.

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Hysingla ER during pregnancy can result in neonatal opioid withdrawal syndrome which may be life-threatening to the neonate if not recognized and treated, and requires management according to protocols developed by neonatology experts.

Interactions with Central Nervous System Depressants

- Hypotension, profound sedation, coma, respiratory depression, or death may result if Hysingla ER is used concomitantly with other CNS depressants, including alcohol or illicit drugs that can cause CNS depression. Start with a lower Hysingla ER dose than usual (i.e., 20-30% less), monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant.

Use in Elderly, Cachectic, and Debilitated Patients and Patients with Chronic Pulmonary Disease

- Closely monitor elderly, cachectic, and debilitated patients, and patients with chronic obstructive pulmonary disease because of the increased risk of life-threatening respiratory depression. Consider the use of alternative non-opioid analgesics in patients with chronic obstructive pulmonary disease if possible.

Use in Patients with Head Injury and Increased Intracranial Pressure

- Monitor patients closely who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or impaired consciousness). Opioids may obscure the clinical course in a patient with a head injury. Avoid the use of Hysingla ER in patients with impaired consciousness or coma.

Hypotensive Effect

- Hysingla ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. Monitor patients during dose initiation or titration. In patients with circulatory shock, Hysingla ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Hysingla ER in patients with circulatory shock.

Gastrointestinal Obstruction, Dysphagia, and Choking

- Use caution when prescribing Hysingla ER for patients who have difficulty swallowing, or have underlying gastrointestinal disorders that may predispose them to obstruction, dysphagia, or choking. Consider use of an alternative analgesic in these patients.

Decreased Bowel Motility

- Hysingla ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of Hysingla ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Hydrocodone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis.

Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of CYP3A4 inhibitors may prolong opioid effects. Use with CYP3A4 inducers may cause lack of efficacy or development of withdrawal symptoms. If co-administration is necessary, evaluate patients frequently and consider dose adjustments until stable drug effects are achieved.

Driving and Operating Machinery

- Hysingla ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

Interaction with Mixed Agonist/Antagonist Opioid Analgesics

- Avoid the use of mixed agonist/antagonist analgesics in patients who have received or are receiving Hysingla ER, as they may reduce the analgesic effect and/or precipitate withdrawal.

QTc Interval Prolongation

- QTc prolongation has been observed following daily doses of 160 mg of Hysingla ER. Avoid use in patients with congenital QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong QTc interval. In patients who develop QTc prolongation, consider reducing the dose.

ADVERSE REACTIONS

- Most common treatment-emergent adverse reactions (≥5%) reported by patients treated with Hysingla ER in the clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence.

References:

1. Acetaminophen Prescription Combination Drug Products with more than 325 mg: FDA Statement – Recommendation to Discontinue Prescribing and Dispensing. US Food and Drug Administration. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm381650.htm. Updated January 14, 2014. Accessed January 22, 2016.

2. *Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling.* US Department of Health and Human Services, Food and Drug Administration and Center for Drug Evaluation and Research. April 2015.

Please see Additional Warnings and Precautions on the preceding pages.

Please read Brief Summary of Full Prescribing Information on the following pages, including Boxed Warning.

Hysingla™ ER

(Hydrocodone Bitartrate) II

EXTENDED-RELEASE TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details please see the Full Prescribing Information and Medication Guide.)

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

Addiction, Abuse, and Misuse

HYSINGLA™ ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing HYSINGLA ER, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of HYSINGLA ER. Monitor for respiratory depression, especially during initiation of HYSINGLA ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving HYSINGLA ER tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of HYSINGLA ER with all cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving HYSINGLA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.11), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

4 CONTRAINDICATIONS HYSINGLA ER is contraindicated in patients with: • Significant respiratory depression • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected paralytic ileus and gastrointestinal obstruction • Hypersensitivity to any component of HYSINGLA ER or the active ingredient, hydrocodone bitartrate

5 WARNINGS AND PRECAUTIONS 5.1 Addiction, Abuse, and Misuse HYSINGLA ER contains hydrocodone, a Schedule II controlled substance. As an opioid, HYSINGLA ER exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9.1)]*. As extended-release products such as HYSINGLA ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed HYSINGLA ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing HYSINGLA ER, and monitor all patients receiving HYSINGLA ER for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of HYSINGLA ER for the proper management of pain in any given patient. Abuse or misuse of HYSINGLA ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death *[see Drug Abuse and Dependence (9.1), and Overdosage (10)]*. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing HYSINGLA ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product. **5.2 Life-Threatening Respiratory Depression** Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10.2)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of HYSINGLA ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with HYSINGLA ER and following dose increases. To reduce the risk of respiratory depression, proper dosing and titration of HYSINGLA ER are essential *[see Dosage and Administration (2.1, 2.2)]*. Overestimating the HYSINGLA ER dose when converting patients from another opioid product can result in fatal overdose with the first dose. Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone. **5.3 Neonatal Opioid Withdrawal Syndrome** Prolonged use of HYSINGLA ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. **5.4 Interactions with Central Nervous System Depressants** Hypotension, profound sedation, coma, respiratory depression, and death may result if HYSINGLA ER is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). When considering the use of HYSINGLA ER in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin HYSINGLA ER is made, start with a lower HYSINGLA ER dose than usual (i.e., 20-30% less), monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.2)]*. **5.5 Use in Elderly, Cachectic, and Debilitated Patients** Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating HYSINGLA ER and when HYSINGLA ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*. **5.6 Use in Patients with Chronic Pulmonary Disease** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with HYSINGLA ER, as in these patients, even usual therapeutic doses of HYSINGLA ER may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible. **5.7 Use in Patients with Head Injury and Increased Intracranial Pressure** In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. Monitor patients closely who may be susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury. Avoid the use of HYSINGLA ER in patients with impaired consciousness or coma. **5.8 Hypotensive Effect** HYSINGLA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Monitor these patients for signs of hypotension after initiating or titrating the dose of HYSINGLA ER. In patients with circulatory shock, HYSINGLA ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of HYSINGLA ER in patients with circulatory shock. **5.9 Gastrointestinal Obstruction, Dysphagia, and Choking** In the clinical studies with specific instructions to take HYSINGLA ER with adequate water to swallow the tablet, 11 out of 2476 subjects reported difficulty swallowing HYSINGLA ER. These reports included esophageal obstruction, dysphagia, and choking, one of which had required medical intervention to remove the tablet *[see Adverse Reactions (6)]*. Instruct patients not to pre-soak, lick, or otherwise wet HYSINGLA ER tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*. Patients with underlying gastrointestinal disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying gastrointestinal disorders resulting in a small gastrointestinal lumen. **5.10 Decreased Bowel Motility** HYSINGLA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of HYSINGLA ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Hydrocodone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis. **5.11 Cytochrome P450 3A4 Inhibitors and Inducers** Since the CYP3A4 isoenzyme plays a major role in the metabolism of HYSINGLA ER, drugs that alter CYP3A4 activity may cause changes in clearance of hydrocodone which could lead to changes in hydrocodone plasma concentrations. The clinical results with CYP3A4 inhibitors show an increase in hydrocodone plasma concentrations and possibly increased or prolonged opioid effects, which could be more pronounced with concomitant use of CYP3A4 inhibitors. The expected clinical result with CYP3A4 inducers is a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration is necessary, caution is advised when initiating HYSINGLA ER treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.1)]*. **5.12 Driving and Operating Machinery** HYSINGLA ER may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Peak blood levels of hydrocodone may occur 14 – 16 hours (range 6 – 30 hours) after initial dosing of HYSINGLA ER tablet administration. Blood levels of hydrocodone, in some patients, may be high at the end of 24 hours after repeated-dose administration. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of HYSINGLA ER and know how they will react to the medication *[see Clinical Pharmacology (12.3)]*. **5.13 Interaction with Mixed Agonist/Antagonist Opioid Analgesics** Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received, or are receiving, a course of therapy with a full opioid agonist analgesic, including HYSINGLA ER. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. **5.14 QTc Interval Prolongation** QTc prolongation has been observed with HYSINGLA ER following daily doses of 160 mg *[see Clinical Pharmacology (12.2)]*. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing HYSINGLA ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. HYSINGLA ER should be avoided in patients with congenital long QT syndrome. In patients who develop QTc prolongation, consider reducing the dose by 33 – 50%, or changing to an alternate analgesic.

6 ADVERSE REACTIONS The following serious adverse reactions are described elsewhere in the labeling: • Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]* • Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]* • Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]* • Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]* • Hypotensive Effects *[see Warnings and Precautions (5.8)]* • Gastrointestinal Effects *[see Warnings and Precautions (5.9, 5.10)]* **6.1 Clinical Trial 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. A total of 1,827 patients were treated with HYSINGLA ER in controlled and open-label chronic pain clinical trials. Five hundred patients were treated for 6 months and 364 patients were treated for 12 months. The clinical trial population consisted of opioid-naïve and opioid-experienced patients with persistent moderate to severe chronic pain. The common adverse reactions (≥2%) reported by patients in clinical trials comparing HYSINGLA ER (20-120 mg/day) with placebo are shown in Table 2 below:

Table 2: Adverse Reactions Reported in ≥2% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Naïve and Opioid-Experienced Patients

	Open-label Titration Period	Double-blind Treatment Period	
MedDRA Preferred Term	(N=905) (%)	Placebo (N=292) (%)	HYSINGLA ER (N=296) (%)
Nausea	16	5	8
Constipation	9	2	3
Vomiting	7	3	6
Dizziness	7	2	3
Headache	7	2	2
Somnolence	5	1	1
Fatigue	4	1	1
Pruritus	3	<1	0
Tinnitus	2	1	2
Insomnia	2	2	3
Decreased appetite	1	1	2
Influenza	1	1	3

The adverse reactions seen in controlled and open-label chronic pain studies are presented below in the following manner: most common (≥5%), common (≥1% to <5%), and less common (<1%).

The most common adverse reactions (≥5%) reported by patients treated with HYSINGLA ER in the chronic pain clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, somnolence.

The common (≥1% to <5%) adverse events reported by patients treated with HYSINGLA ER in the chronic pain clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were:

Ear and labyrinth disorders	tinnitus
Gastrointestinal disorders	abdominal pain, abdominal pain upper, diarrhea, dry mouth, dyspepsia, gastroesophageal reflux disease
General disorders and administration site conditions	chest pain, chills, edema peripheral, pain, pyrexia

Infections and infestations	bronchitis, gastroenteritis, gastroenteritis viral, influenza, nasopharyngitis, sinusitis, urinary tract infection
Injury, poisoning and procedural complications	fall, muscle strain
Metabolism and nutrition disorders	decreased appetite
Musculoskeletal and connective tissue disorders	arthralgia, back pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity
Nervous system disorders	lethargy, migraine, sedation
Psychiatric disorders	anxiety, depression, insomnia
Respiratory, thoracic and mediastinal disorders	cough, nasal congestion, oropharyngeal pain
Skin and subcutaneous tissue disorders	hyperhidrosis, pruritus, rash
Vascular disorders	hot flush, hypertension

Other less common adverse reactions that were seen in <1% of the patients in the HYSINGLA ER chronic pain clinical trials include the following in alphabetical order: abdominal discomfort, abdominal distention, agitation, asthenia, choking, confusional state, depressed mood, drug hypersensitivity, drug withdrawal syndrome, dysphagia, dyspnea, esophageal obstruction, flushing, hypogonadism, hypotension, hypoxia, irritability, libido decreased, malaise, mental impairment, mood altered, muscle twitching, edema, orthostatic hypotension, palpitations, presyncope, retching, syncope, thinking abnormal, thirst, tremor, and urinary retention.

7 DRUG INTERACTIONS 7.1 Drugs Affecting Cytochrome P450 Isoenzymes *Inhibitors of CYP3A4* Co-administration of HYSINGLA ER with ketoconazole, a strong CYP3A4 inhibitor, significantly increased the plasma concentrations of hydrocodone. Inhibition of CYP3A4 activity by inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. Caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. *Inducers of CYP3A4* CYP3A4 inducers may induce the metabolism of hydrocodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration with HYSINGLA ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. **7.2 Central Nervous System Depressants** The concomitant use of HYSINGLA ER with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and HYSINGLA ER for signs of respiratory depression, sedation and hypotension. When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Warnings and Precautions (5.4)]*. **7.3 Interactions with Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics** Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist analgesics (buprenorphine) may reduce the analgesic effect of HYSINGLA ER or precipitate withdrawal symptoms in these patients. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving HYSINGLA ER. **7.4 MAO Inhibitors** HYSINGLA ER is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between hydrocodone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate. **7.5 Anticholinergics** Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation in addition to respiratory and central nervous system depression when HYSINGLA ER is used concurrently with anticholinergic drugs. **7.6 Strong Laxatives** Concomitant use of HYSINGLA ER with strong laxatives (e.g., lactulose), that rapidly increase gastrointestinal motility, may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. If HYSINGLA ER is used in these patients, closely monitor for the development of adverse events as well as changing analgesic requirements.

8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy *Pregnancy Category C Risk Summary* There are no adequate and well-controlled studies of HYSINGLA ER use during pregnancy. Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. In animal reproduction studies with hydrocodone in rats and rabbits no embryotoxicity or teratogenicity was observed. However, reduced pup survival rates, reduced fetal/pup body weights, and delayed ossification were observed at doses causing maternal toxicity. In all of the studies conducted, the exposures in animals were less than the human exposure (see Animal Data). HYSINGLA ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Clinical Considerations* Fetal/neonatal adverse reactions Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*. *Data* Animal Data No evidence of embryotoxicity or teratogenicity was observed after oral administration of hydrocodone throughout the period of organogenesis in rats and rabbits at doses up to 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). However, in these studies, reduced fetal body weights and delayed ossification were observed in rat at 30 mg/kg/day and reduced fetal body weights were observed in in rabbit at 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). In a pre- and post-natal development study pregnant rats were administered oral hydrocodone throughout the period of gestation and lactation. At a dose of 30 mg/kg/day decreased pup viability, pup survival indices, litter size and pup body weight were observed. This dose is approximately 0.1-fold the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons. **8.2 Labor and Delivery** Opioids cross the placenta and may produce respiratory depression in neonates. HYSINGLA ER is not recommended for use in women immediately prior to and during labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. HYSINGLA ER may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. **8.3 Nursing Mothers** Hydrocodone is present in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue HYSINGLA ER, taking into account the importance of the drug to the mother. Infants exposed to HYSINGLA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped. **8.4 Pediatric Use** The safety and effectiveness of HYSINGLA ER in pediatric patients have not been established. Accidental ingestion of a single dose of HYSINGLA ER in children can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*. HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) when exposed to water or other fluids. Pediatric patients may be at increased risk of esophageal obstruction, dysphagia, and choking because of a smaller gastrointestinal lumen if they ingest HYSINGLA ER *[see Warnings and Precautions (5.9)]*. **8.5 Geriatric Use** In a controlled pharmacokinetic study, elderly subjects (greater than 65 years) compared to young adults had similar plasma concentrations of hydrocodone *[see Clinical Pharmacology (12.3)]*. Of the 1827 subjects exposed to HYSINGLA ER in the pooled chronic pain studies, 241 (13%) were age 65 and older (including those age 75 and older), while 42 (2%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received HYSINGLA ER. Hydrocodone may cause confusion and oversedation in the elderly. In addition, because of the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease and concomitant use of CNS active medications, start elderly patients on low doses of HYSINGLA ER and monitor closely for adverse events such as respiratory depression, sedation, and confusion. **8.6 Hepatic Impairment** No adjustment in starting dose with HYSINGLA ER is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*. **8.7 Renal Impairment** No dose adjustment is needed in patients with mild renal impairment. Patients with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations than those with normal renal function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in these patients and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE 9.1 Controlled Substance HYSINGLA ER contains hydrocodone bitartrate, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, abuse, addiction and criminal diversion. The high drug content in the extended-release formulation adds to the risk of adverse outcomes from abuse and misuse. **9.2 Abuse** All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get "high," or the use of steroids for performance enhancement and muscle build up. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal. "Drug-seeking" behavior is very common to addicts and drug abusers. Drug seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers, people with untreated addiction, and criminals seeking drugs to sell. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction. HYSINGLA ER can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by law, is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk is increased with concurrent use of HYSINGLA ER with alcohol or other central nervous system depressants. *Risks Specific to Abuse of HYSINGLA ER* HYSINGLA ER is for oral use only. Abuse of HYSINGLA ER poses a risk of overdose and death.. Taking cut, broken, chewed, crushed, or dissolved HYSINGLA ER increases the risk of overdose and death. With parenteral abuse, the inactive ingredients in HYSINGLA ER can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV. Abuse Deterrence Studies *Summary* The *in vitro* data demonstrate that HYSINGLA ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the *in vitro* data, also indicate that HYSINGLA ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of HYSINGLA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate. HYSINGLA ER contains hydrocodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, addiction, and criminal diversion *[See Warnings and Precautions (5.1) and Drug Abuse and Dependence (9)]*. **9.3 Dependence** Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects. Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. HYSINGLA ER should be discontinued by a gradual downward titration *[see Dosage and Administration (2.6)]*. If HYSINGLA ER is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.3)]*.

10 OVERDOSAGE 10.1 Symptoms Acute overdosage with opioids is often characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. **10.2 Treatment** In the treatment of HYSINGLA ER overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from opioid overdosage. Nalmefene is an alternative opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of HYSINGLA ER may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling, as needed, to maintain adequate respiration. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on HYSINGLA ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

CAUTION
DEA FORM REQUIRED

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

U.S. Patent Numbers: 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

This brief summary is based on Hysingla ER Prescribing Information 303511-0C, Revised 02/2015 (A)

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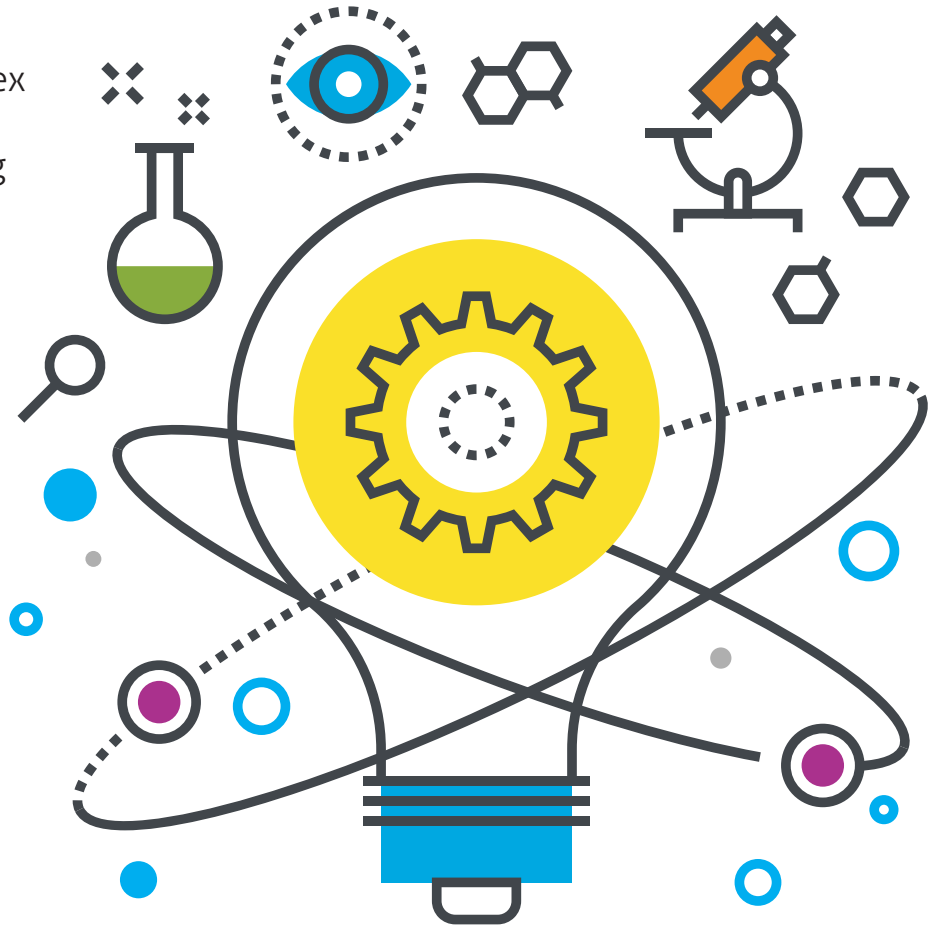

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The Evolving Treatment Landscape for Melanoma

Scott McClelland, PharmD, Senior Director of Pharmacy, Florida Blue

Scott McClelland
PharmD

Melanoma, the most serious form of skin cancer, occurs when unrepaired deoxyribonucleic acid (DNA) damage to skin cells triggers mutations, causing skin cells to rapidly multiply, thereby resulting in malignant tumor formation.[1] Although the etiology of melanoma is unknown, several risk factors have been identified in the development of melanoma: ultraviolet (UV) light exposure (primarily UV-B), fair complexion, presence of multiple moles, personal and family history of melanoma, specific genetic conditions (e.g., xeroderma pigmentosum, retinoblastoma), and a weakened immune system caused by medical treatments or certain diseases.[1,2]

With early detection, melanoma is highly treatable; however, once melanoma has spread to distant organs, it can become extremely difficult to treat and may be associated with a poor prognosis.[2,3] In 2012, 67,753 people in the United States were diagnosed with invasive melanoma.[2] The American Cancer Society (ACS) estimates that in 2016, approximately 76,380 new cases of melanoma will be diagnosed and 10,130 people will die of melanoma.[2,4] Recent innovations in the areas of detection and treatment have resulted in increased numbers of early-stage diagnoses and extended survival rates. It is important to note, however, that these new treatments are accompanied by higher costs and increased rates of serious adverse events, both of which must be taken into consideration when making treatment selection and prescription coverage decisions.

Current Treatment Guidelines

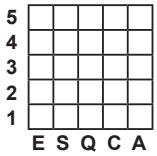
Prevention remains the best strategy for reducing the risk of developing melanoma.[5] Preventive strategies include the regular use of sunscreen; wearing protective clothing, wide-brimmed hats, and sunglasses; seeking shade; limiting the amount of time spent outdoors during peak UV radiation hours; and avoiding indoor tanning beds.[5] While prevention is ideal, it is not always possible, nor does it guarantee that an individual will not develop melanoma. Therefore, early detection and treatment of melanoma are crucial for achieving optimal health outcomes.[5]

The American Joint Committee on Cancer (AJCC) provides descriptions of tumor staging and the American Cancer Society supplements this information with the accompanying survival rates, which are detailed in Table 1.[6,7] Treatment selection, with surgery, immunotherapy, and/or targeted drugs, depends on staging, patient-specific factors, tumor-specific characteristics, and drug safety profiles, particularly toxicity profiles. The 2016 National Comprehensive Cancer Network (NCCN) melanoma treatment guidelines note that the best management strategy for any patient with cancer is through participation in a clinical trial. NCCN guidelines also suggest that surgical excision remains the first-line treatment for all stages of melanoma, although excision is not always feasible due to the presence of certain comorbidities or cosmetically sensitive tumor locations.[8] Tumor removal can be performed through local excision, wide local excision, lymphadenectomy, or sentinel lymph node biopsy.

Adjuvant treatment is recommended for some patients with stage IB or II melanoma and for patients with stage III or IV melanoma. Adjunctive therapies include: chemotherapy, biochemotherapy (combination of chemotherapy with cytokine therapy), radiation therapy, immunotherapy, and targeted therapy.[1] In patients with stable IB or II melanoma, adjuvant treatment typically involves observation or interferon alfa (IFNα) (category 2B recommendation).[8]

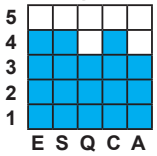
Figure 1. NCCN Evidence Blocks Categories and Definitions[11]

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Often provides long-term survival advantage or has curative potential
4	**Very effective:** Sometimes provides long-term survival advantage or has curative potential
3	**Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
2	**Minimally effective:** Modest, no, or unknown impact on survival and sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs is common
2	**Moderately toxic:** Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1	**Highly toxic:** Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** Several well-designed randomized trials
3	**Average quality:** Low quality randomized trials or well-designed non-randomized trials
2	**Low quality:** Case reports or clinical experience only
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients; lower quality trials whether randomized or not
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

For patients with stage III melanoma, treatment depends on whether patients have sentinel node positive disease or clinically positive nodes. Adjuvant treatment for stage III, sentinel positive disease involves observation, IFNα, or high-dose ipilimumab (Yervoy®, Bristol-Myers Squibb) (category 2B), while adjuvant treatment for stage III, clinically positive node(s) disease includes the aforementioned sentinel-positive disease recommendations or biochemotherapy (category 2B).[8]

Stage III in-transit disease adjuvant pharmacotherapy involves intralesional injections with talimogene laherparepvec (Imlygic™, Amgen) (category 1) or Bacillus Calmette–Guérin (BCG), IFN, or interleukin-2 (IL-2) (all category 2B); topical imiquimod (Aldara, Graceway Pharmaceuticals LLC); isolated limb infusion/perfusion (ILI/ILP) with melphalan (Alkeran®, GlaxoSmithKline, LLC); or systemic therapy. Systemic therapy may include immunotherapy with pembrolizumab (Keytruda®, Merck), nivolumab (Opdivo®, Bristol-Myers Squibb), or nivolumab/ipilimumab; or targeted therapy with dabrafenib (Tafinlar®, Novartis)/trametinib (Mekinist®, Novartis), vemurafenib (Zelboraf®, Genentech)/cobimetinib (Cotellic™, Genentech), vemurafenib, or dabrafenib in certain patients.

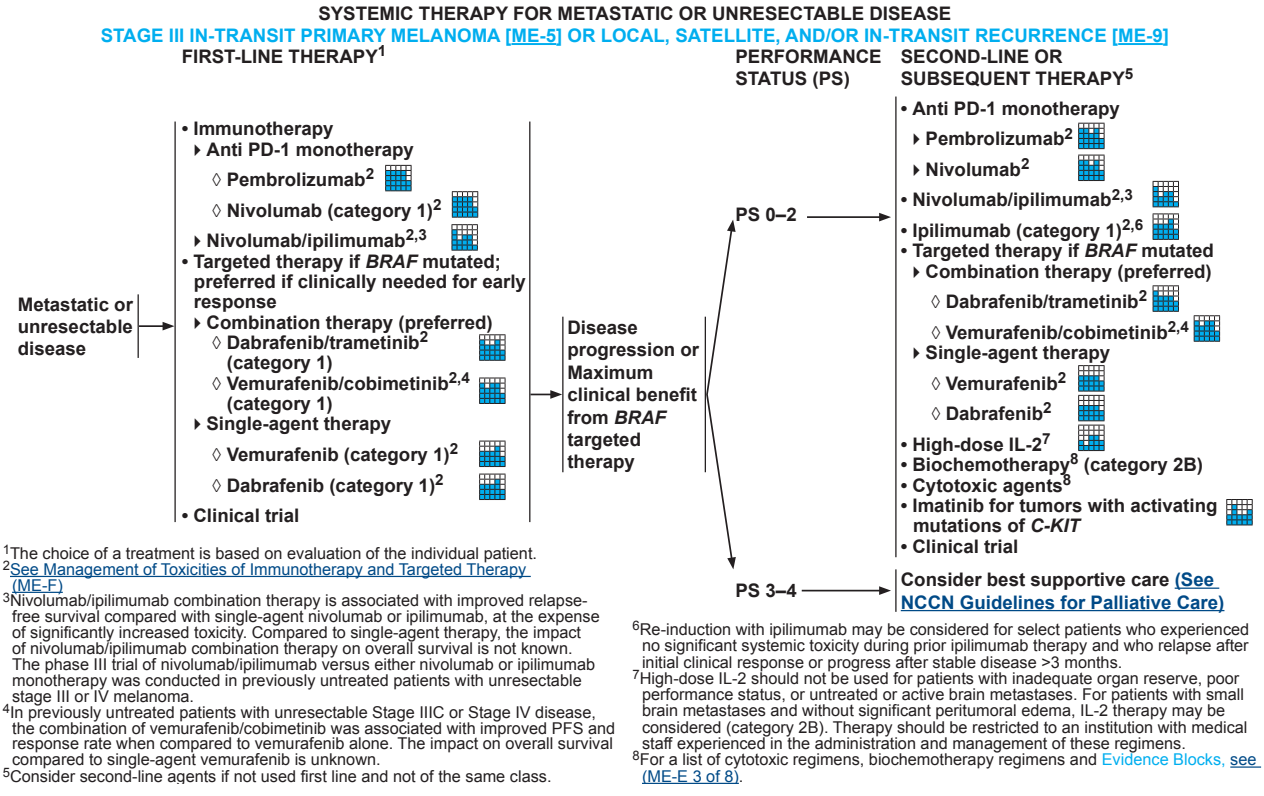
Following disease progression or maximal clinical benefit from targeted therapy, second-line or subsequent therapy options include the aforementioned agents or high-dose IL-2, biochemotherapy, cytotoxic agents, or imatinib (Gleevec, Novartis) in patients with certain tumor types. Of note, chemotherapy treatments are of limited value in most patients with stage IV melanoma, and management strategies differ depending on whether the distant metastatic disease is limited (resectable) or disseminated (unresectable).[1,8]

Table 2 highlights the various Food and Drug Administration (FDA)-approved treatments for adjuvant therapy, along with the associated costs. It is important to note that this table gives the reader an idea of the costs associated with different treatments, this does not represent all strengths.

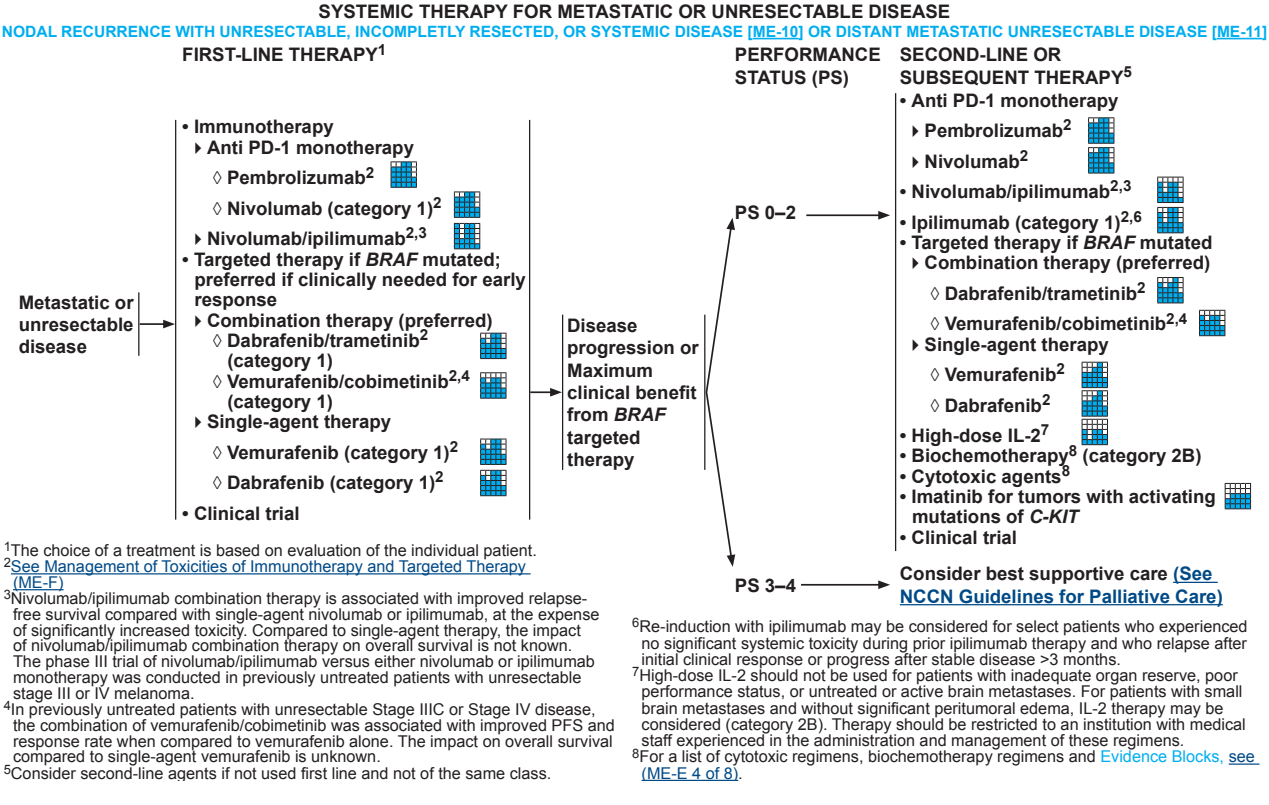
Product Landscape and Recent Treatment Innovations

Until recently, there had been little progress in the development of additional metastatic melanoma treatment options, and the initial treatment options, whether used alone or as part of a combination regimen, did not provide

Figure 2. Treatments for Unresectable or Metastatic Melanoma and Their Accompanying NCCN Evidence Blocks[11]



[1]The choice of a treatment is based on evaluation of the individual patient.
[2]See Management of Toxicities of Immunotherapy and Targeted Therapy (ME-F)
[3]Nivolumab/ipilimumab combination therapy is associated with improved relapse-free survival compared with single-agent nivolumab or ipilimumab, at the expense of significantly increased toxicity. Compared to single-agent therapy, the impact of nivolumab/ipilimumab combination therapy on overall survival is not known. The phase III trial of nivolumab/ipilimumab versus either nivolumab or ipilimumab monotherapy was conducted in previously untreated patients with unresectable stage III or IV melanoma.
[4]In previously untreated patients with unresectable Stage IIIC or Stage IV disease, the combination of vemurafenib/cobimetinib was associated with improved PFS and response rate when compared to vemurafenib alone. The impact on overall survival compared to single-agent vemurafenib is unknown.
[5]Consider second-line agents if not used first line and not of the same class.
[6]Re-induction with ipilimumab may be considered for select patients who experienced no significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or progress after stable disease >3 months.
[7]High-dose IL-2 should not be used for patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. For patients with small brain metastases and without significant peritumoral edema, IL-2 therapy may be considered (category 2B). Therapy should be restricted to an institution with medical staff experienced in the administration and management of these regimens.
[8]For a list of cytotoxic regimens, biochemotherapy regimens and Evidence Blocks, see (ME-E 3 of 8).



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[8]For a list of cytotoxic regimens, biochemotherapy regimens and Evidence Blocks, see (ME-E 4 of 8).

substantial improvements in progression-free survival (PFS) or overall survival (OS).[9] Prior to 2011, the one-year survival rate for patients diagnosed with metastatic melanoma was as low as 33 percent, with a median overall survival of approximately nine months.[9] Until 2011, the only systemic treatments for metastatic melanoma with FDA approval included dacarbazine (DTIC-Dome®) and IL-2.[3]

The discovery of genetic modifications that result in tumor transformation and melanoma progression has resulted in the development of individualized, targeted treatment options.[3] Since 2011, seven monotherapies and three combination therapies received FDA approval, drastically increasing the number of available treatments.[3] Two examples of innovations in the treatment of metastatic melanoma include the discoveries of BRAF inhibition (BRAFi) and combined BRAF/MEK inhibition (BRAFi/MEKi).[3] These innovations focus on such mutations, as 40 to 60 percent of oncogenic driver mutations in melanoma are due to mutations in the BRAF gene.[3] BRAF inhibitors include dabrafenib and vemurafenib and MEK inhibitors include cobimetinib and trametinib.

In clinical trials conducted among previously untreated patients with metastatic melanoma, treatment with vemurafenib or dabrafenib was associated with a vast improvement in overall and progression-free survival (PFS) compared with dacarbazine; however, treatment with dabrafenib was associated with less severe adverse reactions.[8] Trametinib, an oral, small molecule inhibitor of MEK1 and MEK2, has also shown improvement in PFS in clinical trials compared to patients who received traditional chemotherapy, and treatment with trametinib has not been associated with secondary skin lesions.[8]

The introduction of these aforementioned kinase inhibitors and the immune checkpoint inhibitor ipilimumab, an anti-CTLA-4 antibody, has substantially improved the prognosis of metastatic melanoma. More recently, clinical trials evaluating the efficacy of the programmed death receptor-1 (PD-1) inhibitors nivolumab and pembrolizumab have demonstrated further improvements in overall survival (OS) in patients with metastatic melanoma.[9]

Despite a high initial response rate, nearly half of patients with metastatic melanoma relapse after six months when treated with a targeted monotherapy.[8] Treatment with ipilimumab and nivolumab has demonstrated that combination treatment approaches may boost response rates; however, the toxicity profiles of combination regimens

Table 1. Stages of Melanoma and Survival Rates[1,7]

Stage	Description	5-Year Survival (%)	10-Year Survival (%)
IA	Less than 1.0mm in thickness, is not ulcerated, and has a mitotic rate of less than 1/mm^2. It has not been found in lymph nodes or distant organs.	97	95
IB	Less than 1.0mm in thickness and is ulcerated or has a mitotic rate of at least 1/mm^2, or it is between 1.01 and 2.0mm and is not ulcerated. It has not been found in lymph nodes or distant organs.	92	86
IIA	Between 1.01 and 2.0mm in thickness and is ulcerated, or it is between 2.01 and 4.0mm and is not ulcerated. It has not been found in lymph nodes or distant organs.	81	67
IIB	Between 2.01 and 4.0mm in thickness and is ulcerated, or it is thicker than 4.0mm and is not ulcerated. It has not been found in lymph nodes or distant organs.	70	57
IIC	Thicker than 4.0mm and is ulcerated. It has not been found in lymph nodes or distant organs.	53	40
IIIA	Any thickness, but not ulcerated. It has spread to one to three lymph nodes near the affected skin area, but the nodes are not enlarged and the melanoma is found only when they are viewed under the microscope. There is no distant spread.	78*	68*
IIIB	Any thickness and is ulcerated. It has spread to one to three lymph nodes near the affected skin area, but the nodes are not enlarged and the melanoma is found only when they are viewed under the microscope. There is no distant spread.	59	43
IIIC	Any thickness and is ulcerated. It has spread to one to three lymph nodes near the affected skin area. The nodes are enlarged because of the melanoma. There is no distant spread.	40	24
IV	Has spread beyond the original area of skin and nearby lymph nodes to other organs such as the lung, liver, or brain, or to distant areas of the skin, subcutaneous tissue, or distant lymph nodes. Neither spread to nearby lymph nodes nor thickness is considered in this stage, but typically the melanoma is thick and has also spread to the lymph nodes.	15–20	10–15

**The survival rate is higher for stage IIIA cancers than for some stage II cancers. This is likely because the main (primary) tumor is often less advanced for IIIA cancers, although this is not clear.*

must be carefully evaluated when considering the use of a combination regimen.[3] Of note, there are ongoing clinical trials comparing the safety and efficacy of a variety of combination regimens with BRAFi and MEKi or an anti-CTLA-4 antibody.[8]

Treatment Innovations and Implications for Managed Care

The annual cost of skin cancer treatment in the United States is $8.1 billion, with $3.3 billion attributable directly to melanoma. Furthermore, between 2002 and 2006 and from 2007 to 2011, the average annual cost of melanoma treatment increased by 288 percent, compared with a 25 percent increase for all other cancers combined.[4] Indirect annual morbidity and mortality costs associated with melanoma, including lost productivity, are estimated to be $39.2 million and $3.3 billion, respectively. Furthermore, each potentially preventable melanoma death causes an additional 15 years of potential life lost, which contributes to the social, economic, and human toll of this disease.[4]

The introduction of individualized, targeted therapies to the previously limited treatment landscape has resulted in significant improvements in the overall health outcomes and survival of patients with metastatic melanoma; however, these improved outcomes and survival rates are accompanied by higher costs. In addition to the cost of the individual metastatic melanoma treatments, the management of treatment-induced adverse effects also results in increased overall health care costs, as these adverse effects may result in the need for hospitalization or management of symptoms.[10]

Until the recent availability of the NCCN Evidence Blocks publication, oncologist-developed guidelines did not incorporate cost into the overall treatment recommendations. Using a scale of 1 to 5, the NCCN Evidence Blocks rate each agent or regimen on the following factors: efficacy, safety, quality of evidence, consistency of evidence, and affordability (see Figure 1).[11] The individual treatments for unresectable or metastatic melanoma and their accompanying NCCN Evidence Blocks are listed in Figure 2.

The Evidence Blocks in Figure 2 suggest that, although the affordability of the newer treatments is low, and even lower for the newer combination regimens, the efficacy of these treatments is considered moderate or high. It is also important to note that the level of safety of the individual agents is typically moderate or high; however, when evaluating combination regimens, the safety rating tends to decline to a lower level, due to the increase in adverse effects associated with the concomitant administration of the individual agents.[11]

Another oncology-focused group, the American Society of Clinical Oncology (ASCO), has begun to incorporate value into its treatment recommendations.[12] ASCO has developed a "value framework" that uses data collected from a prospective randomized trial to compare a newly available oncology treatment to the previous standard of care for an individual indication.[12] This framework is then used to generate a "net health benefit" score that takes into consideration the cost of treatment and, thus, may be useful in assessing the value of each available treatment option.[12] With the emphasis shifting away from efficacy alone and moving toward a decision-making model that incorporates cost and demonstrated value, payors have begun incorporating the above guidelines into their coverage decision-making process and are becoming more aware of the potential for value-based payment to become part of their payment structure.[12]

Future Directions

While treatment-associated improvements in PFS and OS have been made over the last few years, significant opportunities for further treatment advancements remain. The continued research and development of additional treatments should focus on further extending PFS and OS rates, while also seeking to develop treatments with more favorable toxicity profiles. Currently, there are various investigational agents being studied in phase 2 and 3 trials, including the MEK inhibitor binimetinib; the BRAF inhibitor encorafenib; the programmed death ligand-1 (PD-L1) inhibitors atezolizumab and durvalumab; two novel vaccines, eltrapuldencel-T and seviprotimut-L; and the oncolytic immunotherapeutic strain administered intralesionally or intravenously, coxsackievirus A21.[13]

Despite these recent and potential treatment advancements, prevention still remains the cornerstone of reducing the risk of developing melanoma. Prevention techniques aimed at reducing melanoma incidence have the potential to substantially decrease melanoma-related costs by an estimated $250 million per year.[4] In addition to paying close attention to the current treatment landscape and pharmaceutical agents in the pipeline, payors should also be mindful of the need for increased education among patients regarding melanoma prevention, which may mitigate the risk of developing melanoma and thereby avoid the need for melanoma treatment altogether. Lastly, due to the recent commencement of the Center for Medicare and Medicaid Innovation (CMMI) Oncology Care Model (OCM) on July 1, 2016, payors are now highly focused on providing higher quality care at lower costs, which will certainly involve an emphasis on thoughtful treatment selection.

Table 2. FDA-Approved Drugs for Melanoma and Associated Costs[1,8]

Drug Brand Name	Drug Generic Name	Category/Description	Wholesale Acquisition Cost (WAC) Per Dose*
Proleukin®	Aldesleukin	Recombinant IL-2; immune response regulator	$2,894.00
Intron A®	Recombinant IFNα-2b	Exhibits antiproliferative effects including suppression of cell proliferation	$1,200.11 (for 50 million IU injection)
PegIntron®	Peg IFNα-2b	Pleiotropic cytokine	$789.69 (for 80mcg kit)
Tafinlar®	Dabrafenib	Inhibitor of RAF kinases; indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	$9,369.82 (for 75 mg tablets, quantity = 120)
Zelboraf®	Vemurafenib	Inhibitor of RAF kinases; indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	$5,425.40 (for 240mg tablets, quantity = 120)
Mekinist®	Trametinib	Reversible inhibitor of MEK1 and MEK2 activation and of MEK1 and MEK2 kinase activity	$10,272.77 (for 2mg tablets, quantity = 30)
Cotellic®	Cobimetinib	Highly selective MEK1 and MEK2 kinase inhibitor	$6,061.76 (for 20mg tablets, quantity = 63)
Yervoy®	Ipilimumab	Fully human recombinant anti-CTLA-4 monoclonal antibody (IgG1κ)	$6,758.96 (for 5mg/mL, total of 10mL solution)
Opdivo®	Nivolumab	Potent, highly selective, fully humanized immunoglobulin (Ig) G4-kappa monoclonal antibody against PD-1	$2,470.48 (for 10mg/mL, total of 10mL solution)
Keytruda®	Pembrolizumab	Potent, highly selective, fully humanized immunoglobulin (Ig) G4-kappa monoclonal antibody against PD-1	$4,380.74 (for 25mg/mL, total of a 4mL solution)
DTIC-Dome®	Dacarbazine	Prodrug converted by demethylation to cytostatic agent. The antineoplastic effect is due to an inhibition of cell growth and DNA synthesis.	No price listed

**Micromedex. Red Book Online.*

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Survey Offers Clues to Improved Management of Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) currently affects about 35 million Americans. Currently the seventh most commonly made diagnosis by primary care physicians, IBS causes recurring abdominal pain, constipation and/or diarrhea in those with the disease. In the absence of a clear pathophysiological abnormality, diagnosis of IBS relies on patient-reported symptoms.[1] The diagnosis of IBS usually occurs after physicians rule out other possible diseases. The accuracy of diagnosis has benefited from the recognition of IBS-specific symptom criteria, known as the Rome Criteria.

There are two common types of IBS — IBS with constipation (IBS-C) and IBS with diarrhea (IBS-D). Sufferers may experience both types and the degree to which IBS impacts a patient's life can vary from disruptive annoyance to disabling symptoms.

A recent survey conducted by the American Gastroenterological Association (AGA) of patients with both diagnosed and undiagnosed IBS-C or IBS-D regarding their experiences with IBS symptoms revealed that 67 percent of patients with IBS-C and IBS-D reported having symptoms for more than a year before seeing a physician regarding the condition.[2] Patients did, on the other hand, report having previously discussed symptoms with family or friends — 80 percent of the time. A key aspect of IBS is the variability in symptoms, with IBS sufferers reporting symptoms would come and go. A majority of IBS-C and IBS-D patient indicated they could predict symptoms on a daily basis, but 22 percent of respondents indicated they were not at all able to accurately predict whether they might experience symptoms on a given day. When reflecting upon symptom-free episodes, most IBS-C and IBS-D patients indicated that symptom-free periods usually lasted for a few days or less.[2]

Notably, IBS sufferers participating in the AGA survey indicated that symptoms resulted in two missed days of school or work and nine days of impacted productivity per month. Additionally, respondents indicated that IBS symptoms interfere with daily life, as a majority of diagnosed IBS-C and IBS-D patients experience symptoms at least four to six days out of the week.[2]

The GI symptoms most bothersome for IBS-C patients is constipation while for IBS-D patients find loss of bowel control and fecal incontinence most bothersome. Overall, over half of survey respondents reported that IBS symptoms are extremely or very bothersome to their quality of life.[2]

The AGA survey revealed that in patients suffering from IBS-C the most common treatments included taking fiber, non-prescription laxatives, stool softeners, home remedies and increasing exercise. Most IBS-C sufferers who took laxatives and stool softeners did not report limiting the frequency with which these products were utilized. Significantly, less than a quarter of IBS-C sufferers were very satisfied with their treatment options.[2]

IBS-D sufferers reported utilizing treatments such as Imodium, fiber, Pepto Bismol, exercising, and Gas-X to achieve symptom relief. Over-the-counter therapies were reported as being taken by 77 percent of patients as a means of attempting to manage symptoms.[2]

Since there is no one known cause of IBS, there is no one treatment for the syndrome. Treatment of IBS varies, depending on the patient and the severity of their symptoms. Antispasmodics remain first-line drugs in the treatment of IBS-D, despite probable anticholinergic side effects.[3] Other treatment strategies may include antidiarrheal agents, laxatives, receptor-targeted drugs, probiotics, antibiotics and some psychiatric treatments. Multi-disciplinary approaches to treatment are often most effective in achieving symptom relief.[4]

Newer treatments for IBS-C include Amitiza® (lubiprostone), a gastrointestinal chloride-channel activator that increases intestinal motility and facilitation of stool passage, and Linzess® (linoclotide), an agonist of guanylate cyclase that was found to have significant effects on ascending colonic transit time and clinical symptoms related to stooling.[4] In some individuals with IBS-D the use of rifaximin, an antibiotic therapy, has proven beneficial.[4]

A recently approved treatment for IBS-D, Viberzi™ (eluxadoline), activates receptors in the nervous system that can lessen bowel contractions, slowing movement through the colon and reducing colon sensitivity.[5] In clinical trials, this new therapy reduced two major symptoms of IBS-D, including diarrhea and abdominal pain. [5] Viberzi may be an option for effective long-term treatment and maintenance therapy in the management of IBS-D symptoms.

In light of the reported reluctance of patients to discuss IBS symptoms with physicians, the lack of consistent causes of this condition, and the variations in symptoms and severity, there have been challenges to the effective management of IBS. However, opportunities to improve the symptoms and complications associated with IBS exist — by improving patient and provider communication and by appropriately integrating new IBS-specific therapies into the strategies for management of IBS patients, in order to improve the quality of life and reduce symptoms in sufferers.

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For Your Patients With IBS-D

Does the Threat of Diarrhea and Abdominal Pain Keep Looming?

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

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

Indication

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

Important Safety Information

Contraindications

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

Warnings and Precautions

Sphincter of Oddi Spasm:

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

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

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

Be Proactive Against IBS-D

VIBERZI: Lasting Relief of Diarrhea and Abdominal Pain*

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

- Based on nonclinical data

VIBERZI provides sustained efficacy against diarrhea and abdominal pain

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

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

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

Important Safety Information

Warnings and Precautions (continued)

Sphincter of Oddi Spasm (continued):

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

Pancreatitis:

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

Adverse Reactions

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

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

Visit ViberziHCP.com to learn more

Viberzi™
(eluxadoline) tablets CIV
75 mg • 100 mg

Be Proactive Against IBS-D

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

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

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

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

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

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

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

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

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

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Revised: June 2015 ELX32306 - A - 05/15

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

The first **NEW** treatment for PBC in nearly 20 years[1]

OCALIVA™
obeticholic acid

Introducing a First-in-Class Treatment for Primary Biliary Cholangitis

Activate the Power Within

PBC, primary biliary cholangitis.

Indication

OCALIVA™ (obeticholic acid) is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information

Contraindications

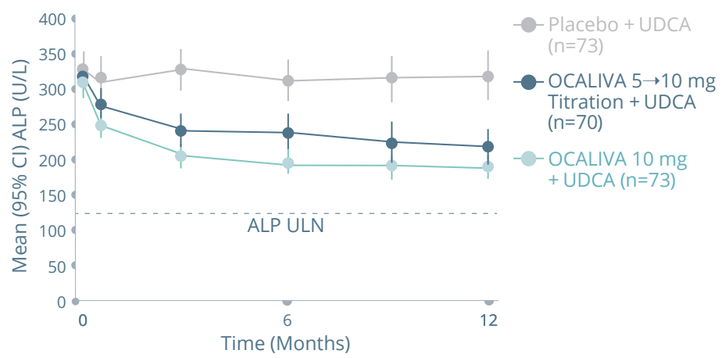
OCALIVA is contraindicated in patients with complete biliary obstruction.

Please see Important Safety Information and brief summary of Full Prescribing Information on following pages. Rx only.

OCALIVA™
obeticholic acid

Delivered Significant, Sustained Reductions in Alkaline Phosphatase[2]

Mean Alkaline Phosphatase Over 12 Months[2,a]



[a]In the trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.

ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

New, for patients with PBC who have had an inadequate response for at least 1 year or are intolerant to UDCA[2]

- OCALIVA is a farnesoid X receptor (FXR) agonist that works differently than UDCA[1,2]
  - — FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways[2]
- 46% of patients taking OCALIVA + UDCA met the primary endpoint vs 10% of patients taking UDCA alone[2,b]
  - — OCALIVA is also effective as monotherapy[c] in patients who are intolerant to UDCA
  - — Pruritus was the most common adverse event
- OCALIVA is taken orally once daily, with a recommended starting dose of 5 mg, which if tolerated after 3 months, should be up-titrated to 10 mg[2]

[b]In a randomized, double-blind, placebo-controlled, 12-month study of 216 adults with PBC who had taken UDCA for ≥12 months (stable dose for ≥3 months) and had an inadequate response or who were intolerant to UDCA and did not receive it for ≥3 months. Primary composite endpoint was the percentage of patients achieving alkaline phosphatase <1.67x ULN, an alkaline phosphatase decrease of ≥15%, and total bilirubin ≤ ULN.[2]

[c]In a pooled analysis of data from the pivotal trial and from a separate randomized, double-blind, placebo-controlled, 3-month study (N=51), more patients taking OCALIVA (38%) achieved a response with regard to the primary endpoint vs the placebo group (4%).[2]

Interconnect™ SUPPORT SERVICES

Your Patients. Our Commitment.

From enrollment to insurance—including our **$0 co-pay program**[d]—Interconnect provides support to assist your office and help your patients start and stay on OCALIVA. Visit **interconnectsupport.com** or call **1-844-622-4278** to get your patients started.

[d]For patients with commercial insurance.

Want to learn more about how to take PBC treatment further with OCALIVA? Please visit **ocalivahcp.com**.

To learn more about Intercept Pharmaceuticals, Inc., please visit **interceptpharma.com**.

Important Safety Information

Warnings and Precautions

Liver-Related Adverse Reactions

Dose-related, liver-related adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flare have been observed in clinical trials, as early as one month after starting treatment with OCALIVA 10 mg once daily up to 50 mg once daily (up to 5-times the highest recommended dosage). Monitor patients during treatment with OCALIVA for elevations in liver biochemical tests and for the development of liver-related adverse reactions. Weigh the potential risks against the benefits of continuing treatment with OCALIVA in patients who have experienced serious liver-related adverse reactions. The maximum recommended dosage of OCALIVA is 10 mg once daily. Adjust the dosage for patients with moderate or severe hepatic impairment. Discontinue OCALIVA in patients who develop complete biliary obstruction.

Severe Pruritus

Severe pruritus was reported in 23% of patients in the OCALIVA 10 mg arm, 19% of patients in the OCALIVA titration arm, and 7% of patients in the placebo arm in a 12 month double-blind randomized controlled trial that consisted of 216 patients. Severe pruritus consists of intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical interventions. Management strategies include the addition of bile acid resins or antihistamines, OCALIVA dosage reduction, and/or temporary interruption of OCALIVA dosing.

Reduction in HDL-C

Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high-density lipoprotein-cholesterol (HDL-C). Dose-dependent reductions from baseline in mean HDL-C levels were observed at 2 weeks in OCALIVA-treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to OCALIVA after 1 year at the highest tolerable, recommended dosage (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.

Adverse Reactions

The most common adverse reactions from subjects taking OCALIVA (≥5%) were pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema.

Drug Interactions

- **Bile Acid Binding Resins**
  Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of OCALIVA. If taking a bile acid binding resin, take OCALIVA at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible.
- **Warfarin**
  The International Normalized Ratio (INR) is decreased following co-administration of warfarin and OCALIVA. Monitor INR and adjust the dose of warfarin, as needed, to maintain the target INR range when co-administering OCALIVA and warfarin.
- **CYP1A2 Substrates with Narrow Therapeutic Index**
  Obeticholic acid, the active ingredient in OCALIVA, may increase the exposure to concomitant drugs that are CYP1A2 substrates. Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g. theophylline and tizanidine) is recommended when co-administered with OCALIVA.

Please see brief summary of Full Prescribing Information for OCALIVA (obeticholic acid) 5 mg and 10 mg tablets on following pages.

To report SUSPECTED ADVERSE REACTIONS, contact Intercept Pharmaceuticals, Inc. at 1-844-782-ICPT or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References: 1. URSO [package insert]. Bridgewater, NJ: Aptalis Pharma US, Inc.; 2013.
2. OCALIVA [package insert]. New York, NY: Intercept Pharmaceuticals, Inc.; 2016.

Intercept
450 W 15th Street, Suite 505 | New York, NY 10011 | T: 844-782-4278 | F: 646-747-1001

Brief Summary of Prescribing Information for OCALIVA (obeticholic acid)
OCALIVA (obeticholic acid) tablets, for oral use
See package insert for Full Prescribing Information.

INDICATIONS AND USAGE: OCALIVA™ is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP) *[see Clinical Studies (14) in Full Prescribing Information]*. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. **CONTRAINDICATIONS:** OCALIVA is contraindicated in patients with complete biliary obstruction. **WARNINGS AND PRECAUTIONS: Liver-Related Adverse Reactions:** In two 3-month, placebo-controlled clinical trials a dose-response relationship was observed for the occurrence of liver-related adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flare with dosages of OCALIVA of 10 mg once daily to 50 mg once daily (up to 5-times the highest recommended dosage), as early as one month after starting treatment with OCALIVA *[see Overdosage]*. In a pooled analysis of three placebo-controlled trials in patients with PBC, the exposure-adjusted incidence rates for all serious and otherwise clinically significant liver-related adverse reactions, and isolated elevations in liver biochemical tests, per 100 patient exposure years (PEY) were: 5.2 in the OCALIVA 10 mg group (highest recommended dosage), 19.8 in the OCALIVA 25 mg group (2.5 times the highest recommended dosage) and 54.5 in the OCALIVA 50 mg group (5 times the highest recommended dosage) compared to 2.4 in the placebo group. Monitor patients during treatment with OCALIVA for elevations in liver biochemical tests and for the development of liver-related adverse reactions. Weigh the potential risks against the benefits of continuing treatment with OCALIVA in patients who have experienced clinically significant liver-related adverse reactions. The maximum recommended dosage of OCALIVA is 10 mg once daily *[see Dosage and Administration (2.1) in Full Prescribing Information]*. Adjust the dosage for patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Discontinue OCALIVA in patients who develop complete biliary obstruction *[see Contraindications]*. **Severe Pruritus:** Severe pruritus was reported in 23% of patients in the OCALIVA 10 mg arm, 19% of patients in the OCALIVA titration arm, and 7% of patients in the placebo arm in Trial 1, a 12-month double-blind randomized controlled trial of 216 patients *[see Adverse Reactions]*. Severe pruritus was defined as intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical interventions. In the subgroup of patients in the OCALIVA titration arm who increased their dosage from 5 mg once daily to 10 mg once daily after 6 months of treatment (n=33), the incidence of severe pruritus was 0% from Months 0 to 6 and 15% from Months 6 to 12. The median time to onset of severe pruritus was 11, 158, and 75 days for patients in the OCALIVA 10 mg, OCALIVA titration, and placebo arms, respectively. Management strategies include the addition of bile acid resins or antihistamines, OCALIVA dosage reduction, and/or temporary interruption of OCALIVA dosing *[see Dosage and Administration (2.2) in Full Prescribing Information]*. **Reduction in HDL-C:** Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high density lipoprotein-cholesterol (HDL-C). In Trial 1, dose-dependent reductions from baseline in mean HDL-C levels were observed at 2 weeks in OCALIVA-treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. At month 12, the reduction from baseline in mean HDL-C level was 19% in the OCALIVA 10 mg arm, 12% in the OCALIVA titration arm, and 2% in the placebo arm. Nine patients in the OCALIVA 10 mg arm, 6 patients in the OCALIVA titration arm, versus 3 patients in the placebo arm had reductions in HDL-C to less than 40 mg/dL. Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to OCALIVA after 1 year at the highest recommended dosage that can be tolerated (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment. **ADVERSE REACTIONS:** The following clinically significant adverse reactions are described elsewhere in labeling: • Liver-Related Adverse Reactions *[see Warnings and Precautions]* • Severe Pruritus *[see Warnings and Precautions]* • Reduction in HDL-C *[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. A total of 432 patients with PBC were studied in three double-blind placebo-controlled trials. Of these patients, 290 were treated with OCALIVA for at least 6 months, 232 were treated for at least 12 months, and 70 were treated for at least 2 years. There were 131 patients who received OCALIVA 10 mg once daily and 70 who received OCALIVA 5 mg once daily. In Trial 1, 216 patients were randomized (1:1:1) to receive either: • OCALIVA 10 mg once daily for the entire 12 months of the trial (n=73); • OCALIVA titration (5 mg once daily for the initial 6 months, with the option to increase to 10 mg once daily for the last 6 months, in patients who were tolerating OCALIVA, but had ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction) (n=70); or • placebo (n=73). During the trial, OCALIVA or placebo was administered in combination with UDCA in 93% of patients and as monotherapy in 7% of patients who were unable to tolerate UDCA. The overall discontinuation rate was 12% in the OCALIVA 10 mg arm, 10% in the OCALIVA titration arm, and 4% in the placebo arm. The recommended starting dosage of OCALIVA is 5 mg orally once daily for 3 months with titration to 10 mg once daily based upon tolerability and response *[see Dosage and Administration (2.1) in Full Prescribing Information]*. Initiation of therapy with OCALIVA 10 mg once daily is not recommended due to an increased risk of pruritus. The most common adverse reactions in Trial 1 occurring in at least 5% of patients in either OCALIVA treatment arm and at an incidence at least 1% higher than the placebo treatment arm are shown in Table 1.

Table 1: Most Common Adverse Reactions in Adult Patients with PBC in Trial 1 by Treatment Arm with or without UDCA[a]

Adverse Reaction[b]	OCALIVA 10 mg N = 73 %	OCALIVA Titration[c] N = 70 %	Placebo N = 73 %
Pruritus[d]	70	56	38
Fatigue[e]	25	19	15
Abdominal pain and discomfort[f]	10	19	14
Rash[g]	10	7	8
Arthralgia	10	6	4
Oropharyngeal pain	8	7	1
Dizziness[h]	7	7	5
Constipation	7	7	5
Peripheral Edema	7	3	3
Palpitations	7	3	1
Pyrexia	7	0	1
Thyroid function abnormality[i]	4	6	3
Eczema	3	6	0

[a] In the trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.
[b] Occurring in greater than or equal to 5% of patients in either OCALIVA treatment arm and at an incidence greater than or equal to1% higher than in the placebo treatment arm.
[c] Patients randomized to OCALIVA titration received OCALIVA 5 mg once daily for the initial 6 month period. At Month 6, patients who were tolerating OCALIVA, but had an ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction were eligible for titration from 5 mg once daily to 10 mg once daily for the final 6 months of the trial.
[d] Includes skin eruptions, prurigo, pruritus, pruritus generalized, eye pruritus, ear pruritus, anal pruritus, vulvovaginal pruritus, and rash pruritic.
[e] Includes fatigue, tiredness and asthenia.
[f] Includes abdominal pain upper, abdominal pain, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.
[g] Includes urticaria, rash, rash macular, rash papular, rash maculo-papular, heat rash, urticaria cholinergic.
[h] Includes dizziness, syncope, presyncope.
[i] Includes thyroxine free decreased, blood thyroid stimulating hormone increased, hypothyroidism.

Liver-Related Adverse Reactions: In Trial 1, the following serious or otherwise clinically significant liver-related adverse reactions were reported at the recommended dosage of OCALIVA: one patient in the OCALIVA 10 mg treatment arm experienced ascites; one patient in the OCALIVA titration treatment arm experienced two episodes of ascites and four episodes of hepatic encephalopathy; one patient in the placebo treatment arm experienced variceal bleeding. Pruritus: Approximately 60% of patients had a history of pruritus upon enrollment in Trial 1. Treatment-emergent pruritus, including all the terms described in Table 1, generally started within the first month following the initiation of treatment with OCALIVA. The incidence of pruritus was higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration arm, 70% and 56%, respectively. Discontinuation rates due to pruritus were also higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration arm, 10% and 1%, respectively. The number of patients with pruritus who required an intervention (e.g., dosage adjustment, treatment interruption, or initiation of bile acid binding resin or antihistamine) was 30 of 51 patients (59%) in the OCALIVA 10 mg arm, 24 of 39 patients (62%) in the OCALIVA titration arm, and 14 of 28 patients (50%) in the placebo arm. **DRUG INTERACTIONS: Bile Acid Binding Resins:** Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of OCALIVA. If taking a bile acid binding resin, take OCALIVA at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible *[see Dosage and Administration (2.4) in Full Prescribing Information]*. **Warfarin:** The International Normalized Ratio (INR) decreased following coadministration of warfarin and OCALIVA *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range when co-administering OCALIVA and warfarin. **CYP1A2 Substrates with Narrow Therapeutic Index:** Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g. theophylline and tizanidine) is recommended when co-administered with OCALIVA. **USE IN SPECIFIC POPULATIONS: Pregnancy:** Risk Summary: The limited available human data on the use of obeticholic acid during pregnancy are not sufficient to inform a drug-associated risk. In animal reproduction studies, no developmental abnormalities or fetal harm was observed when pregnant rats or rabbits were administered obeticholic acid during the period of organogenesis at exposures approximately 13 times and 6 times human exposures, respectively, at the maximum recommended human dose (MRHD) of 10 mg *[see Data below]*. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data: *Animal Data:* In an embryo-fetal development study in rats, obeticholic acid was administered orally during the period of organogenesis at doses of 5, 25, and 75 mg/kg/day. At 25 mg/kg/day (a dose that produced systemic exposures approximately 13 times those in humans at the MRHD of 10 mg), there was no maternal or developmental toxicity. At 75 mg/kg/day (approximately 40 times the human exposure at the MRHD), decreased fetal body weights and increased numbers of early or late resorptions and nonviable fetuses were observed. In maternal animals, mortality, fetal loss, decreased body weight and food consumption as well as decreased body weight gain were observed at 75 mg/kg/day. Thus, the developmental toxicity observed at this dose may be secondary to maternal toxicity. In rabbits, obeticholic acid was administered orally during the period of organogenesis at doses of 3, 9, and 20 mg/kg/day. Obeticholic acid administered at doses up to 20 mg/kg/day (approximately 6 times the human exposure at the MRHD) was not teratogenic and did not produce any evidence of fetal harm. In a pre- and post-natal development study, administration of obeticholic acid in rats during organogenesis through lactation at doses of 5, 25, and 40 mg/kg/day did not produce effects on pregnancy, parturition or postnatal development at any dose (the 40 mg/kg/day dose is approximately 21 times the human exposure at the MRHD). Obeticholic acid exposure margins were calculated using systemic exposure (AUC) values of obeticholic acid plus obeticholic acid's active metabolite conjugates (tauro-obeticholic acid and glyco-obeticholic acid) in animals (at the indicated doses) and in humans at the MRHD of 10 mg. **Lactation:** Risk Summary: There is no information on the presence of obeticholic acid in human milk, the effects on the breast-fed 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 OCALIVA and any potential adverse effects on the breastfed infant from OCALIVA or from the underlying maternal condition. **Pediatric Use:** The safety and effectiveness of OCALIVA in pediatric patients have not been established. **Geriatric Use:** Of the 201 patients in clinical trials of OCALIVA who received the recommended dosage (5 mg or 10 mg once daily), 41 (20%) were 65 years of age and older, while 9 (4%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and subjects less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** Plasma exposure to obeticholic acid and its active conjugates, increases significantly in patients with moderate to severe hepatic impairment (Child-Pugh Classes B and C) *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Monitor patients during treatment with OCALIVA for elevations in liver biochemical tests and for the development of liver-related adverse reactions *[see Warnings and Precautions]*. Dosage adjustment of OCALIVA is recommended for patients with moderate and severe hepatic impairment *[see Dosage and Administration (2.3) in Full Prescribing Information]*. No dosage adjustment is needed in patients with mild hepatic impairment (Child-Pugh Class A). **OVERDOSAGE:** In PBC patients who received OCALIVA 25 mg once daily (2.5 times the highest recommended dosage) or 50 mg once daily (5 times the highest recommended dosage), a dose-dependent increase in the incidence of liver-related adverse reactions, including elevations in liver biochemical tests, ascites, jaundice, portal hypertension, and primary biliary cholangitis flare, was reported *[see Warnings and Precautions]*. In the case of overdosage, patients should be carefully observed and supportive care administered, as appropriate. **PATIENT COUNSELING INFORMATION:** Liver-Related Adverse Reactions: • Advise patients to report any symptoms of worsening of liver disease to their healthcare provider immediately and that they may need to undergo laboratory testing periodically while on OCALIVA treatment to assess liver function *[see Warnings and Precautions]*. • Advise patients who develop symptoms of complete biliary obstruction to report to their healthcare provider immediately *[see Contraindications]*. Severe Pruritus: • Advise patients to contact their healthcare provider if they experience pruritus or an increase in the severity of pruritus *[see Warnings and Precautions]*. Reduction in HDL-C: • Advise patients that they may need to undergo laboratory testing to check for changes in lipid levels while on treatment with OCALIVA *[see Warnings and Precautions]*. Administration: Advise patients to take: • OCALIVA with or without food. • OCALIVA at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible *[see Drug Interactions]*.

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New York, NY 10011

Targeted Therapies May Bring Paradigm Change in Asthma Management

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Overview of Disease State

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RPh

Between 1999 and 2009, the number of asthma-related deaths has decreased by 27 percent, and from 2003 to 2010, the number of asthma-related hospitalizations has decreased by 24 percent.[1] Despite these improvements in rates of asthma-related deaths and hospitalizations, the prevalence rate of asthma is increasing. Following a plateau, the lifetime prevalence rates of asthma have begun to rise and have increased by an annual average of 2.7 percentage points.[1] Historically, the standard treatment for asthma has remained inhaled corticosteroids (ICSs), which suppress multiple inflammatory mechanisms; however, recent development of biologics and targeted therapy may offer new clinical pathways to improve management of this chronic disease.

More than 17 million adults and 6 million children in the United States suffer from asthma.[2] Nearly 45 percent of those with asthma report one or more asthma exacerbations, characterized by coughing, wheezing, shortness of breath or trouble breathing, and chest tightness or pain.[3] Triggers for asthma exacerbations include allergens, exercise, occupational hazards, smoke from tobacco, air pollution and airway infections.[4]

Asthma affects all races and ages, but data from the Centers for Disease Control and Prevention (CDC) reveal that a number of demographic and socioeconomic factors impact asthma rates. Specifically, women are more likely to have asthma than men, and boys are more likely to have asthma than girls.[4] Other influences include a lower level of education and income, smoking, and obesity.[4]

The clinical and economic burdens of asthma are significant. Annually, asthma results in 10.5 million physician office visits and nearly 2 million trips to the emergency department (ED).[2] Annually, asthma deaths, although declining, total more than 3,600, and the disease results in approximately 480,000 hospitalizations.[1,2,4] The annual cost of asthma is $56 billion in medical spending, lost school and work days, and early deaths, with the average yearly cost of care for a child with asthma exceeding $1,000.[4]

Asthma Management

Diagnosing and assessing asthma severity is based on patient history, physical examination, and laboratory findings, and categorized as intermittent, mild persistent, moderate persistent, or severe persistent.[5] Of note, patients diagnosed with any level of asthma may have mild, moderate, or severe exacerbations.

The management of asthma includes treatment of acute asthmatic episodes and control of chronic symptoms, including nocturnal and exercise-induced asthma symptoms. Initiation and scheduling of pharmacologic therapy correspond to the level of asthma severity, with a stepwise approach outlined

both by the National Heart, Lung, and Blood Institute's National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma (GINA).[5,6]

The NAEPP and GINA strategies recommend individualized treatment whereby medications are added to or removed from the regimen as the frequency and severity of symptoms changes. Revised strategies released by GINA in 2016 particularly emphasize a need to move away from a "one-size-fits-all" approach by implementing a control-based asthma management cycle (assess, adjust treatment, and then review response) and taking into account a patient's phenotype or characteristics that may predict risk of exacerbations and/or treatment response.[6]

The general pharmacologic management approach for adults begins with treatment with an as-needed short-acting beta2-agonist (SABA); however, due to the inflammatory nature of asthma, many patients will subsequently require the use of an inhaled corticosteroid (see Table 1).[7] Table 1 gives pricing information for many of the products used to treat asthma, so individuals are given a benchmark for pricing as not all sizes and strengths are included below. When the combination low-dose inhaled corticosteroid/SABA regimen is insufficient to control asthma symptoms, the preferred step-up treatment is to transition to a combination low-dose inhaled corticosteroid/long-acting beta2-agonist (LABA) regimen in combination with an as-needed SABA.[7] Prior to determining whether a regimen should undergo a step-up approach, it is imperative that providers ensure that patients are adhering to treatment and using proper technique.[7]

For patients who achieve and maintain control for approximately three months following this step-up method, a step-down approach can be considered; however, for patients whose asthma persists despite the step-up approach, a medium- or high-dose inhaled corticosteroid/LABA combination can be employed.[7] If asthma still remains uncontrolled with this regimen, add-on therapies may be considered.[7] Add-on treatments include tiotropium (Spiriva®, Boehringer Ingelheim), omalizumab (Xolair®, Genentech), mepolizumab (Nucala®, GlaxoSmithKline), sputum-guided treatment, bronchial thermoplasty, or low-dose oral corticosteroids.[7] Although not mentioned in the 2016 GINA guidelines due to its Food and Drug Administration (FDA) approval occurring after guideline publication, reslizumab (Cinqair®, Teva) may represent a fourth add-on treatment option for patients.[8]

The goals for successful management of asthma include the following:[5]

- Achieve and maintain control of asthma symptoms
- Maintain normal activity levels, including exercise
- Sustain pulmonary function as close to normal as possible
- Prevent asthma exacerbations
- Avoid adverse effects from asthma medications
- Prevent asthma mortality

Biologics for the Treatment of Asthma

Although cornerstone treatments such as inhaled corticosteroids and LABAs provide relief for patients with mild to moderate disease, these therapies may not fully

Table 1: Traditional oral and inhaled asthma medications[7]

Long-term controller medications		
Brand name	**Generic name**	**Wholesale Acquisition Cost (WAC)/per unit***
Inhaled corticosteroids		
Aerospan HFA® 80 mcg/1 actuation, 5.1 gram unit	Flunisolide	$86.27
Alvesco® 80 mcg and 160 mcg, 6.1 gram units	Ciclesonide	$228.91
Arnuity Ellipta® 200 mcg/1 actuation, 30s each	Fluticasone furoate	$200.77
Asmanex® HFA 200 mcg/1 actuation, 13 grams Asmanex Twisthaler® 110 mcg/1 actuation	Mometasone	$210.08 $73.96
Flovent Diskus® 50 mcg/1 actuation Flovent HFA® 0.22 mg/1 actuation, 12 grams	Fluticasone propionate	$150.53 $330.09
Pulmicort® Flexhaler™ 180 mcg/1 actuation Pulmicort Respules® 1 mg/2 mL	Budesonide	$200.47 $615.48
Qvar® 0.08 mg/1 actuation, 8.7 grams	Beclomethasone	$197.99
LABAs		
Foradil®, 0.012 mg, 60 s each	Formoterol, inhaler	$242.96
Perforomist®, 20 mcg/2 mL	Formoterol, solution for nebulizer	$839.07
Serevent Diskus® 0.046/1 actuation	Salmeterol	$322.60
Combination inhaled corticosteroid/LABAs		
Advair Diskus®, 100/50 Advair® HFA, 115/21	Fluticasone and salmeterol	$269.32 $334.63
Breo Ellipta®, 100 mcg/1 actuation – 25 m	Fluticasone and vilanterol	$297.91
Dulera®, 5 mcg/1 actuation, 13 grams	Formoterol and mometasone	$274.43
Symbicort®, 80 mcg/1 actuation, 10.2 grams	Budesonide and formoterol combination	$254.76
Leukotriene modifiers/antagonists		
Accolate® 10 mg or 20 mg, 60 tablets	Zafirlukast	$227.58
Singulair® 10 mg, 30 tablets	Montelukast	$215.40
Zyflo® and Zyflo CR®, 600 mg, 120 tablets	Zileuton	$3,128.04
Miscellaneous		
Spiriva Handihaler®, 18 mcg, 90 s each Spiriva Respimat®, 1.25 mcg and 2.5 mcg, 4 grams	Tiotropium bromide	$1,022.79 $340.93
As-needed, reliever medications: SABAs		
Brand name	**Generic name**	
ProAir®, Proventil®, Ventolin®	Albuterol	$53.02
Xopenex®, 1.25 mg/0.5 mL	Levalbuterol	$204.93

**Micromedex. Red Book Online. 2016*

control more severe asthma.[7] Approximately 5 to 10 percent of patients with asthma have severe disease, and these patients account for approximately half of the total asthma healthcare spend.[9,10] The need for additional treatment options, combined with recent research that shows asthma is a heterogeneous disease spanning many different endotypes and phenotypes, has led to the development of monoclonal antibodies (mAbs) for asthma.[11,12] Three biologics are now available for the treatment of severe asthma: omalizumab (Xolair®, Genentech), mepolizumab (Nucala®, GlaxoSmithKline), and reslizumab (Cinqair®, Teva). These agents target the cells and pathways that trigger the allergic inflammation linked to asthma, see Table 2 for pricing.

Until recently, omalizumab (Xolair) was the only biologic available with an FDA-approved indication for the treatment of asthma. Omalizumab blocks immunoglobulin E (IgE) from binding to the cell receptor and is used as adjunctive therapy with an ICS. Specifically, omalizumab (Xolair) was initially approved for the treatment of adults and adolescents 12 years of age and older with moderate to severe persistent allergic asthma uncontrolled on inhaled corticosteroids, as well as chronic idiopathic urticaria (CIU) uncontrolled by H1 antihistamine treatment.[13] Treatment with omalizumab is indicated in patients who have IgE levels between 30 and 700 IU/mL, a positive skin test or *in vitro* reactivity to a perennial aeroallergen, and whose allergic asthma symptoms are inadequately controlled with an inhaled corticosteroid.[5] Of note, the FDA recently approved omalizumab (Xolair) for use in patients six to 11 years of age with moderate or persistent asthma who meet the aforementioned criteria for use.[14]

Mepolizumab (Nucala) was approved by the FDA in late 2015 as an add-on treatment for patients 12 years of age or older with severe eosinophilic asthma.[15] This interleukin 5 (IL-5) inhibitor reduces severe asthma exacerbations by lowering levels of blood eosinophils, a type of white blood cell that contributes to the development of asthma.[15] Compared with omalizumab which is administered every two or four weeks, mepolizumab is administered subcutaneously once a month by a health care professional in a clinical setting.[13,16]

Table 2: Monoclonal antibody asthma medications[11,12]

Brand name	Generic name	Wholesale Acquisition Cost (WAC)/per unit*
Cinqair®	Reslizumab	$835
Nucala®	Mepolizumab	$2,575
Xolair®	Omalizumab	$945.35

**Micromedex. Red Book Online.*

Reslizumab (Cinqair), the newest biologic available for the treatment of asthma, is an immunoglobulin G (IgG) monoclonal antibody that inhibits interleukin (IL)-5 for patients with eosinophilic asthma. In March 2016, the FDA granted reslizumab approval for the treatment of patients ages 18 years of age and older who have asthma.[17] Reslizumab is administered once every four weeks via intravenous infusion by a health care professional in a clinical setting.[17]

Future Directions

New asthma treatments in development continue to focus on targeting the primary cause of the disease and identifying immunomodulators that provide individualized therapy. In 2015, research that identified the calcium-sensing receptor (CaSR) as playing a role in causing asthma was hailed as a breakthrough.[18] Calcilytics were developed to treat osteoporosis, but could possibly be used to block CaSRs. Clinical trials are necessary, however, to determine whether inhaled calcilytics are safe and effective in treating asthma.

There are a number of asthma biologics now in phase 3 clinical trials, such as AstraZeneca's IL-5 inhibitor benralizumab; Regeneron/Sanofi's IL-4 and IL-13 blocker dupilumab; Roche's IL-13 inhibitor lebrikizumab; and AstraZeneca's IL-13 antibody tralokinumab. AstraZeneca has partnered with Abbott to develop companion diagnostic tests to identify patients who are most likely to benefit from tralokinumab.[19] To date, no companion diagnostic blood tests have been approved for use in asthma.

Recognition that asthma has many variations, such as hypereosinophilic asthma, and that traditional medications do not work for all patients is spurring interest in the detection of biomarkers to select which patients may be appropriate candidates for biologic treatments. Clinical trials have provided evidence that asthma management could move from severity-based to biomarker-based recommendations for medication. The number of eosinophils has been identified as a useful biomarker in dupilumab and mepolizumab, but laboratory standardization of eosinophil blood counts and the mechanisms for reliable use in clinical practice must be established.[20] Serum periostin level is also being studied as a biomarker in clinical trials of lebrikizumab.

Implications for Managed Care

Asthma is a costly disease, and the introduction of biologic therapies is expected to further drive up prescription drug expenditures. Mepolizumab (Nucala) and reslizumab (Cinqair) target eosinophilic airway inflammation, which affects approximately 60 percent of patients with severe asthma, and are expected to generate more than $1 billion in sales during the next five to seven years.[16,17,21] Additionally,

sales of omalizumab are estimated to be nearly $780 million by 2020.[22]

Judicious treatment selection and optimization, with an emphasis on storage and handling, patient monitoring and clinical management, are necessary to ensure the appropriate use of these therapeutic agents. In addition to adhering to FDA-approved indications, payors can maximize health outcomes and cost-effectiveness for these specialty products through the implementation of disease, cost, and utilization management programs. One recent survey of payors found, however, that only 32 percent of payors currently employ a disease management approach for asthma medications and 95 percent require prior authorization for medications.[23] In addition to the recommended strategies above, payors should also explore the various opportunities that may help contain costs, including providing coverage for the biologic treatments under either the pharmacy or the medical benefit and considering value-based contracting or pricing for these newer treatments. As the asthma prevalence rates continue to rise, payors must remain vigilant about controlling asthma-related prescription and medical costs while also preparing for the potential additions to the market with the aforementioned pharmaceutical agents in the pipeline.

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A Novel Approach to Patient Care Optimization Among Individuals with HIV

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Infection with human immunodeficiency virus (HIV), if untreated, leads to acquired immunodeficiency syndrome (AIDS) and premature death. HIV attacks the body's immune system, specifically CD4 cells otherwise known as T cells, which in turn assist the immune system when fighting infections.[1] It has been estimated that there will be 1.39 million new HIV infections in the US from 2015-2035.[2] In 2015, most of the HIV patients will be 50 years old or older.[3] For people living with or at risk for HIV infection, emphasizing these fundamental safeguards will continue to be crucial:[4]

- Knowing their HIV status through routine testing.
- Getting into care soon after HIV diagnosis and starting antiretroviral treatment.
- Remaining in care and staying on HIV treatment.
- Modifying behaviors that reduce the probability of getting or spreading HIV.

Due to the fact that the economic statistics associated with the treatment of HIV are outdated, M. Shah and his colleagues at Johns Hopkins University School of Medicine conducted a cost-effectiveness analysis that incorporated improvements along the HIV care continuum, beyond just testing and treating HIV. According to the analysis, improving engagement in HIV care can improve both epidemiologic impact and overall cost-effectiveness.[2] Therefore, payors and providers should advance their efforts to manage this patient population across the care continuum to reduce costs while optimizing outcomes.

In recent years, antiretroviral therapy (ART) for HIV has become more potent, with fewer side effects and simpler dosing schedules. Over the last decade, the HIV treatment landscape has evolved tremendously, transitioning from complicated cocktail regimens to once-daily, single-tablet regimens (STRs). Achieving viral suppression is associated with improved health outcomes and a lower risk of HIV transmission; however, this also draws attention to various opportunities for improvement within the HIV management and prevention settings.[5]

HIV Treatment Cascade and Treatment as Prevention

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The HIV treatment cascade, or HIV care continuum, encompasses the various steps necessary to provide effective treatment, including testing, linkage to care, retention in care, initiation of ART, and achievement of an undetectable viral load.[1,6] Of the 1.2 million Americans living with HIV, 14 percent of patients were unaware of their HIV status and, therefore, were not accessing the necessary care to stay healthy and reduce the likelihood of transmitting the virus to others. In addition, as shown in Figure 1, only 30 percent were able to reach the goal of being virally suppressed.[7]

Figure 1: Snapshot of Americans Living with HIV[7]

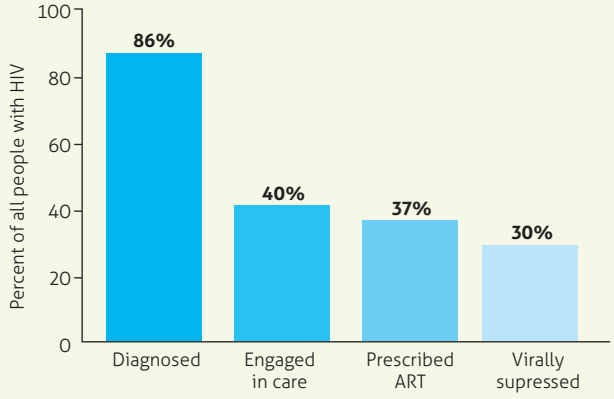


Table 1: The HIV Treatment Landscape[24]			
Drug Class/Generic Name	**Brand Name**	**Generic Availability (Y/N)**	**Wholesale Acquisition Cost (WAC)***
NRTIs			
Abacavir	Ziagen® 300 mg	Y	$482.66
Didanosine	Videx®, Videx® EC 400 mg	Y	$265.48
Emtricitabine	Emtriva® 200 mg	N	$536.52
Lamivudine	Epivir® 150 mg	Y	$225.00
Stavudine	Zerit® 30 mg	Y	$99.65
Tenofovir alafenamide fumarate	Descovy® 200 mg/25 mg	N	$1,466.44
Tenofovir disoproxil fumarate	Viread® 250 mg	N	$924.71
Zidovudine	Retrovir® 100 mg	Y	$151.45
NNRTIs			
Efavirenz	Sustiva® 600 mg	N	$925.11
Etravirine	Intelence® 100 mg	N	$1,090.05
Nevirapine	Viramune®, Viramune® XR 400 mg	Y	$542.53
Rilpivirine	Edurant® 25 mg	N	$895.96
PIs			
Atazanavir	Reyataz® 300 mg	N	$1,367.38
Darunavir	Prezista® 800 mg	N	$1,357.55
Fosamprenavir	Lexiva® 700 mg	N	$1,073.35
Indinavir	Crixivan® 200 mg	N	$456.76
Nelfinavir	Viracept® 250 mg	N	$1,041.97
Saquinavir	Invirase® 200 mg	N	$1,119.96
Tipranavir	Aptivus® 250 mg	N	$1,404.66
Fusion inhibitors			
Enfuvirtide	Fuzeon® 90 mg	N	$3,414.82
Entry inhibitors/CCR5 antagonists			
Maraviroc	Selzentry® 300 mg	N	$1,296.77
INSTIs			
Dolutegravir	Tivicay® 25 mg	N	$711.36
Elvitegravir	Vitekta® 150 mg	N	$1,204.45
Raltegravir	Isentress® 100 mg	N	$321.92
PK boosters			
Cobicistat	Tybost® 150 mg	N	$192.42
Ritonavir**	Norvir® 100 mg	N	$257.17
Combination medications			
Abacavir/lamivudine	Epzicom® 600 mg/300 mg	N	$1,291.71
Abacavir/dolutegravir/lamivudine	Triumeq® 600/50/300 mg	N	$2,407.68
Abacavir/lamivudine/zidovudine	Trizivir® 300/150/300 mg	Y	$1,390.77

Atazanavir/cobicistat	Evotaz® 300/150 mg	N	$1,514.59
Darunavir/cobicistat	Prezcobix® 150/800 mg	N	$1,551.57
Efavirenz/emtricitabine/tenofovir disoproxil fumarate	Atripla® 600/200/300 mg	N	$2,391.55
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate	Genvoya®150/150/200/10 mg	N	$2,577.66
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	Stribild® 150/150/200/30 mg	N	$2,890.54
Emtrictabine/rilpivirine/tenofovir alafenamide fumarate	Odefsey® 200/25/25 mg	N	$2,345.87
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate	Complera® 200/25/300 mg	N	$2,507.74
Emtricitabine/tenofovir alafenamide fumarate	Descovy® 200/25 mg	N	$1,466.44
Emtricitabine/tenofovir disoproxil fumarate	Truvada® 200/300 mg	N	$1,466.44
Lamivudine/zidovudine	Combivir® 150/300 mg	Y	$372.65
Lopinavir/ritonavir	Kaletra® 100/25 mg	N	$230.47

**Micromedex. Red Book Online. 2016*
***Also considered a PI; however, ritonavir is primarily used as a PK booster for PIs*

It is also critical to note that the CDC performed an analysis pertaining to the 70 percent of HIV patients who did not have the virus under control. As seen in Figure 2, among the 840,000 patients who had not achieved viral suppression:[8]

- 20 percent of patients did not know they were infected
- 66 percent had been diagnosed with HIV, but were not receiving regular HIV care
- 4 percent were in HIV care, but were not prescribed an ART
- 10 percent had been prescribed an ART, but had not achieved viral suppression

This further supports the importance of continued and strategic efforts to reach more people with testing and ensure those with HIV receive prompt, continuous care, and treatment in order to help them live longer, healthier lives and prevent the transmission of HIV to others.

Following viral suppression, some patients may achieve HIV patient care optimization, whereby a patient's disease remains well-controlled, with low levels of comorbidities, minor drug-drug interactions (DDIs), minimal issues with polypharmacy, and few problems with treatment resistance. It has been suggested that despite the emphasis on the HIV treatment cascade, only a small proportion of patients with HIV experience optimized care, characterized by effective, uninterrupted ART. Of note, there are various HIV quality measures which monitor whether patients remain in the HIV treatment cascade, including but not limited to the calculated retention rate, retention rate for new patients, use of ART, and an adherence assessment. These quality measures vary across the numerous organizations and differ in their level of impact on a plan's accreditation, incentives, and other pertinent factors.

Engagement in care, which includes both retention in care and adherence to treatment, is an integral component of the HIV treatment cascade and is largely associated with optimal virologic outcomes, including viral suppression.[9] An emphasis on engagement in care may result in an increased number of patients experiencing HIV patient care optimization. Adherence, typically assessed by payors based on proportion of days covered (PDC) or medication possession ratio (MPR), is viewed as an indicator of a patient's engagement in care. Once-daily regimens represent an attractive option, and these regimens have been associated with improved adherence.[10-14] Contributing

Figure 2: Achieving Viral Suppression: More People with HIV Need to be in Medical Care[8]

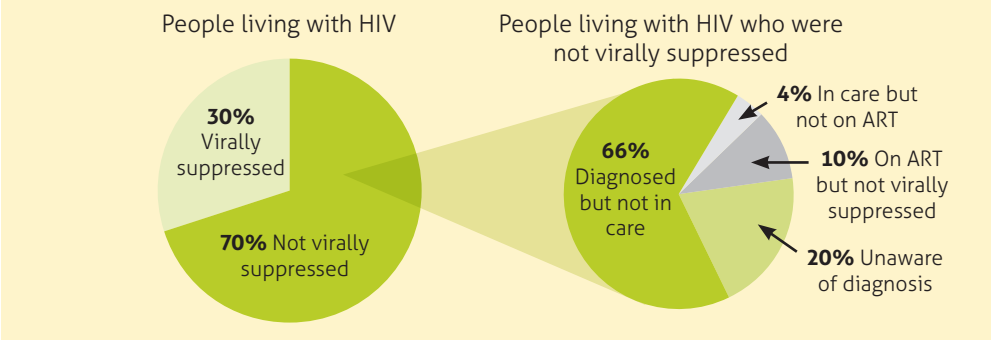


Table 2: Recommended Regimens for ART-Naïve Patients[25]

INSTI-Based Regimens
dolutegravir/abacavir/lamivudine (Triumeq®) (only for patients who are HLA-B*5701 negative) (AI)
dolutegravir (Tivicay®) plus either tenofovir disoproxil fumarate/emtricitabine (Truvada®) (AI) or tenofovir alafenamide fumarate/emtricitabine (Descovy®) (AII)
elvitegravir/cobicistat/tenofovir alafenamide fumarate/emtricitabine (Genvoya®) (AI) or elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine (Stribild®) (AI)
raltegravir (Isentress®) plus either tenofovir disoproxil fumarate/emtricitabine (Truvada®) (AI) or tenofovir alafenamide fumarate/emtricitabine (Descovy®) (AII)
Boosted PI-Based Regimens
darunavir (Prezista®)/ritonavir (Norvir®) plus either tenofovir disoproxil fumarate/emtricitabine (Truvada®) (AI) or tenofovir alafenamide fumarate/emtricitabine (Descovy®) (AII)

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

to poor adherence to treatments are several factors like a poor relationship with their health care provider and dissatisfaction with the healthcare system, as well as the factors listed at right.[15]

Of note, once-daily regimens are associated with favorable safety, tolerability, and effectiveness profiles, as well as high barriers to resistance, reduced potential for DDIs, and a lower incidence of toxicity.[14,16,17] Beyond the aforementioned clinical benefits associated with achieving HIV patient care optimization, there are also financial benefits that can be gained. According to economic model projections, increasing retention in care by 50 percent could result in a 36 percent reduction in HIV transmission (494,000 cases) at $33,700 per quality-adjusted life year (QALY) gained.[2] Although specific data are currently unavailable, it is anticipated that these improvements may have a favorable economic impact upon resource utilization.

In addition to focusing efforts on making improvements at each step of the HIV treatment cascade, another potential strategy exists: treatment as prevention (TasP), which is supported by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC).[18,19,20] The goals of the TasP strategy are to both improve the health of patients with HIV and reduce the risk of transmission to others. Similar to the engagement in care component of the HIV treatment cascade, the success of TasP in preventing onward transmission also relies on ART adherence and retention in care. In the landmark study, HIV Prevention Trials Network 052, early ART initiation resulted in an HIV transmission risk reduction between heterosexual serodiscordant couples by 96 percent.[21]

Pre-exposure prophylaxis, or PrEP, is prophylactic treatment for people who do not have HIV but may be at risk of getting HIV to reduce the risk of getting the virus. Therefore, when someone is exposed to the virus PrEP can work to keep the virus from establishing a permanent infection. When the treatment is taken consistently, PrEP has shown to reduce the risk of HIV infection in people who are at high risk by 92 percent.[22] It is crucial that timely access to treatments be given to patients in order to reduce the number of HIV transmissions. If access is given earlier, payors have the opportunity to reduce the number of HIV transmissions, thus leading to reduced costs of managing these patients had they developed HIV. Figure 3 delineates the potential impact of expanded HIV testing, treatment, and PrEP in the Unites States in four scenarios.[23]

Potential Reasons for Non-Adherence to ART

Patient factors

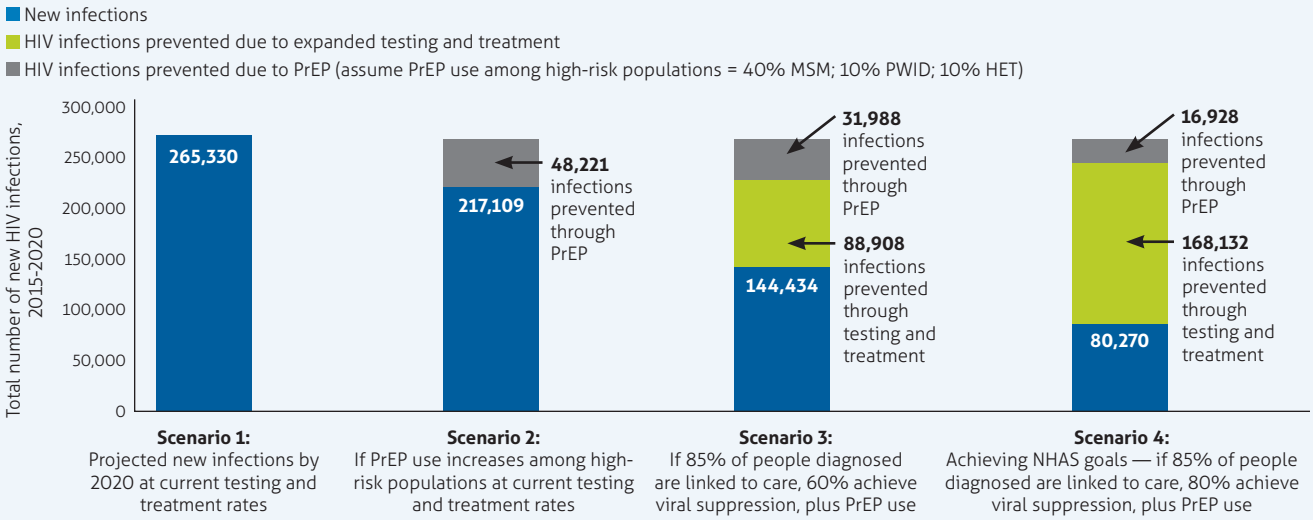
- Drug/alcohol abuse
- Youth
- Race
- Depression
- Low education
- Low confidence in ability to self-medicate
- Extreme anxiety
- Extreme pain
- No change in health status

Medication factors

- Dosing frequency more than BID*
- Pill burden
- Type of drug
- Inability to take medication away from home
- Food requirements
- Side effects

*BID=twice daily

Figure 3: Four Scenarios of the Potential Impact of Expanded HIV Testing, Treatment, and PrEP in the United States, 2015-2020[23]



**MSM= men who have sex with men *PWID= People Who Inject Drugs *HET= Heterosexuals*

These estimations can be utilized to explore the potential impact of interventions to improve engagement in HIV treatment.

Source: Centers for Disease Control and Prevention

Current Treatment Landscape

The HIV treatment landscape is comprised of six drug classes: non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), fusion inhibitors, entry inhibitors/CCR5 antagonists, and integrase strand transfer inhibitors (INSTIs).[24] Table 1 delineates some pricing information for various products used in the treatment of HIV, so individuals can be made aware of approximate costs. When different classes of HIV treatments are combined, the resulting regimen is considered highly active antiretroviral therapy (HAART). The Department of Health and Human Services (DHHS) has published guidelines for the use of ART among adolescents and adults who are infected with HIV-1.[25]

Regarding initial combination regimens for use in ART-naïve patients, the panel recommends the combination of two NRTIs and a third active ART from one of the following classes: an INSTI, NNRTI, or a PI administered with a pharmacokinetic (PK) booster — either cobicistat or ritonavir.[25] Recommended regimens for ART-naïve patients include INSTI-based regimens and PI-based regimens, which are listed in Table 2. Several other regimens exist, including "alternative" and "other" regimen options; however, the focus of this section is to highlight the recommended options, and therefore these additional options will not be listed in table format.

In the setting of virologic failure for treatment-experienced patients, the panel recommends a variety of strategies, including the assessment of adherence, DDIs, drug-food interactions, drug tolerability, HIV ribonucleic acid (RNA) and CD4 T lymphocyte (CD4) cell count trends over time, treatment history, and prior and current drug-resistance testing results.[25] It is recommended that drug-resistance testing be performed while a patient is still taking the failing ART or within four weeks of treatment discontinuation. The goal of treatment for ART-experienced patients who are experiencing virologic failure remains the establishment of virologic suppression.[25] Therefore, the new regimen should include at least two, but preferably three, fully active agents (i.e., an agent that is expected to have uncompromised activity on the basis of the patient's treatment history, drug resistance testing results, and/or the drug's mechanism of action).[25] The panel provides recommendations for both first- and second-line regimen failures; however, due to the wide variation among recommendations based on the type of resistance and the treatment failure(s), the specific recommendations will not be listed in table format.

HIV Pharmaceutical Pipeline

In addition to the tenofovir alafenamide fumarate-containing regimens which recently received Food and Drug Administration (FDA) approval in 2016, there are several agents in the pharmaceutical pipeline for the treatment of HIV. Investigational agents currently in phase 3 clinical trials include doravirine (Merck), bictegravir (Gilead), fostemsavir (ViiV Healthcare/Bristol Myers Squibb), and ibalizumab (TaiMed Biologics).

Doravirine (MK-1439)

Doravirine (Merck) is an investigational NNRTI that is being evaluated as an STR, fixed-dose combination (FDC) regimen with generic tenofovir disoproxil fumarate and lamivudine and could be approved within 2017-2018. Doravirine may provide a potential advantage over already-available NNRTIs as it is neither an inducer nor an inhibitor of major cytochrome P (CYP450) enzymes, including CYP3A4, resulting

in potentially fewer DDIs.[26] Doravirine has also demonstrated *in vitro* activity against common NNRTI resistance mutations and is currently being investigated in a phase 2 clinical trial among patients with treatment-naïve, transmitted NNRTI-resistant HIV.[27,28]

Bictegravir (GS-9883)
A second agent, bictegravir (Gilead), currently in phase 3 trials, may represent a successor of elvitegravir. Bictegravir is an INSTI that does not require boosting and is currently being investigated as an STR that also contains tenofovir alafenamide fumarate and emtricitabine.[29] Of note, an *in vitro* study demonstrated that bictegravir may offer an improved resistance profile compared with dolutegravir, elvitegravir, and raltegravir.[29]

Fostemsavir (BMS-663068)
Fostemsavir (Viiv Healthcare/Bristol Myers Squibb) is an oral product of temsavir, another investigational agent in development, which prevents HIV attachment to host CD4 cells by binding to HIV gp120. Data from an open-label continuation, phase 2b dose-ranging study were reported at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI). At week 96, a greater proportion of patients who received fostemsavir achieved viral loads <50 copies/mL compared to the atazanavir/ritonavir group in the modified intent-to-treat analysis (61 vs. 53 percent, respectively).[30] Of note, in the observed analysis, the proportion of patients achieving viral loads <50 copies/mL was identical for the two treatment arms (90 percent in both arms).[30] This investigational agent is currently being studied in a phase 3 clinical trial among heavily treatment-experienced patients.[31]

Ibalizumab (TMB-355)
Ibalizumab (TaiMed Biologics) is a monoclonal antibody that binds to CD4, thereby blocking HIV entry post-attachment.[32] The FDA granted ibalizumab the orphan drug designation for the treatment of patients with cross-class-resistant HIV.[33] Among the investigational drugs in the HIV pharmaceutical pipeline, ibalizumab represents the only investigational agent that would be administered intravenously, and is being evaluated at doses administered every two or four weeks.[32] Of note, ibalizumab must be administered in combination with an optimized background treatment regimen.[32]

Future Implications

The availability of tenofovir alafenamide fumarate — a newer, safer formulation of tenofovir disoproxil fumarate — as a single-agent product and as part of combination formulations sparked the interest of payers, as this improved formulation offered an improved toxicity profile over its predecessor with a similar price tag. In addition to the aforementioned investigational agents in phase 3 trials, there are a number of other agents currently being studied in phase 1 and phase 2 clinical trials; however, less is known about the potential safety and efficacy of these agents at this time. As additional information regarding these investigational treatments becomes available, payors should remain up to date on these treatment options as they progress through the various phases of the FDA approval process in order to remain prepared for their potential approvals.

Preventing HIV infections is essential to reducing future morbidity and mortality due to HIV infection in the United States. Transmission of HIV is primarily a function of risk behavior and HIV viral load. Interventions at each step of the HIV care continuum (diagnosis, retention in medical care, prescription of antiretroviral therapy [ART], and viral suppression) have the potential to reduce HIV transmission. Patients aware of their HIV infection have lower transmission risk behavior than those infected but unaware of their infection. Regular engagement in medical care is necessary to access ART and achieve viral suppression, which is strongly associated with reduced HIV transmission. In addition, patients engaged in regular medical care are more likely to receive counseling interventions, screening, and treatment for sexually transmitted infections that might reduce HIV transmission.

Also worth noting, HIV-positive people who become infected with hepatitis B virus (HBV) are at increased risk for developing chronic HBV infection and should be tested. In addition, patients who are co-infected with HIV and HBV can have serious medical complications, including an increased risk for liver-related morbidity and mortality. To prevent HBV infection in HIV-infected patients, the Advisory Committee on Immunization Practices recommends universal Hepatitis B vaccination of susceptible patients with HIV/AIDS.[34] In addition, about 25 percent of HIV patients are also infected with hepatitis C virus (HCV). HCV is one of the most important causes of chronic liver disease in the United States and HCV infection progresses more rapidly to liver damage in HIV patients. The U.S. Public Health Service/Infectious Diseases Society of America guidelines recommendation that all HIV patients be screened for HCV infection should be followed.[34] Therefore, the screening and management of this population may be an added cost for payors, and should be considered when managing this patient population.

As previously mentioned, HIV patients who are 50 years old or older present a challenge for providers as these patients tend to have additional comorbidities, are too young to see a geriatrician, and the geriatrician may be less familiar with managing HIV-related treatments. Although HIV specialists are knowledgeable in the distinctions between antiretroviral therapies (ART), they may be less comfortable managing multiple comorbidities.[3] Therefore, in this era of providing care for older patients with HIV, these two medical disciplines are seeing they have much they can learn from one another to coordinate the best care for the patient. This educational deficit is crucial for payors and providers to address in order to transition the best patient care.

Payors may also want to consider shifting their focus toward making improvements in the HIV treatment cascade and implementing the previously mentioned TasP strategy. As new treatments become available, it is likely that treatment-associated costs will continue to rise. As such, it is crucial that payors look to manage costs through the implementation of programs that emphasize the importance of prevention of onward transmission, through retention in care, and medication adherence, as these areas of focus have been identified as targets for potentially large cost-savings opportunities.

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PIPELINE TRENDS

PRODUCT PIPELINE				
Drug	Manufacturer	PDUFA Date	Application Type	Expected Indication
Ocrevus® (ocrelizumab)	Roche Genentech	12/28/2016	BLA	Primary progressive multiple sclerosis; relapsing multiple sclerosis; rheumatoid arthritis
Lutathera® (lutetium Lu 177 dotatate)	Advanced Accelerator Applications	12/28/2016	NDA	Gastroentero-pancreatic neuroendocrine tumors
Solithera IV®	Cempra	12/27/2016	NDA	Community-acquired bacterial pneumonia
Heplisav-B® (hepatitis B vaccine)	Dynavax	12/15/2016	BLA	Hepatitis B
EOquin® (apaziquone)	Spectrum	12/11/2016	NDA	Bladder cancer
LX1032 (telotristat etiprate)	Ipsen; Lexicon Pharmaceuticals	11/30/2016	NDA	Carcinoid syndrome
Brodalumab	AstraZeneca; Valeant	11/16/2016	BLA	Plaque psoriasis; psoriatic arthritis
Tenofovir alafenamide	Gilead Sciences	11/12/2016	NDA	Chronic hepatitis B
Opdivo® (nivolumab)	Bristol-Myers Squibb; Ono Pharmaceutical	11/11/2016	sBLA	Squamous cell carcinoma; liver cancer; urothelial cancer; esophageal junction cancer; gastric cancer; recurrent glioblastoma; nonsquamous non-small cell lung cancer
Enbrel® (etanercept)	Pfizer	11/2/2016	sBLA	Pediatric plaque psoriasis
Jardiance® (empagliflozin)	Boehringer Ingelheim; Eli Lilly	11/2016	sNDA	Reduces cardiovascular mortality in patients with type 2 diabetes; improves glycemic control in patients with type 1 diabetes mellitus
LCS-16 (levonorgestrel)	Bayer	11/2016	NDA	Pregnancy prevention
Sarilumab	Regeneron; Sanofi	10/30/2016	BLA	Rheumatoid arthritis; non-infectious uveitis
Zinplava® (bezlotoxumab)	Merck	10/23/2016	BLA	Prevention of clostridium difficile infection (CDI) recurrence
Rayaldee® (calcifediol)	OPKO Health	10/22/2016	NDA	Secondary hyperpara-thyroidism in adult patients with stage III or IV chronic kidney disease and vitamin D deficiency
Xtandi® (enzalutamide)	Medivation	10/22/2016	sNDA	Metastatic castration-resistant prostate cancer
Tecentriq® (atezolizumab)	Genentech; Roche	10/19/2016	sBLA	Non-small cell lung cancer; kidney cancer; breast cancer; small cell lung cancer; metastatic colorectal cancer; urothelial cancer
SER-120® (low-dose desmopressin nasal spray)	Allergan	10/19/2016	NDA	Adult onset nocturia
AC-170 (cetirizine)	Nicox	10/18/2016	505(b)(2) NDA	Ocular itching associated with allergic conjunctivitis
Arymo ER® (morphine sulfate)	Egalet	10/14/2016	NDA	Pain management
Invokamet XR® (canagliflozin; metformin hydrochloride XR)	Janssen	4Q 2016	NDA	Type 2 diabetes
IVIG-SN (human immunoglobulin)	Green Cross	4Q 2016	BLA	Primary immunodeficiency
NN-1218 (insulin aspart)	Novo Nordisk	4Q 2016	NDA	Type 2 diabetes; type 1 diabetes

PRT-4445 (andexanet alfa)	Portola Pharmaceuticals	4Q 2016	BLA	Reversal of anticoagulation by FXa inhibitors
Stelara® (ustekinumab)	Janssen	4Q 2016	sBLA	Crohn's disease; ankylosing spondylitis; ulcerative colitis; axial spondyloarthritis
Orkambi® (ivacaftor; lumacaftor)	Vertex Pharmaceuticals	9/30/2016	sNDA	Cystic fibrosis patients with two copies of F508del mutation
ABP-501 (biosimilar of Humira®) (adalimumab)	Amgen	9/25/2016	Biosimilar	Psoriatic arthritis; rheumatoid arthritis; juvenile idiopathic arthritis; ulcerative colitis; ankylosing spondylitis; plaque psoriasis; pediatric Crohn's disease; Crohn's disease
Remoxy® (oxycodone)	Durect; Pain Therapeutics	9/25/2016	505(b)(2) NDA	Chronic pain
Yosprala® (aspirin; omeprazole)	Aralez	9/14/2016	NDA	Prevention of cardiovascular disease
GP2015 (biosimilar of Enbrel®) (etanercept)	Sandoz	9/2016	Biosimilar	Psoriatic arthritis; rheumatoid arthritis; juvenile idiopathic arthritis; ankylosing spondylitis; plaque psoriasis
Xeglyze® (abametapir)	Dr. Reddy's; Hatchtech	9/2016	NDA	Head lice infection
Blincyto® (blinatumomab)	Amgen; Onyx	9/1/2016	sBLA	Pediatric Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia; acute lymphoblastic leukemia; non-Hodgkin's lymphoma

PROJECTED BIOSIMILAR LAUNCH DATES		
Biosimilar (Reference Product)	**Brand Manufacturer**	**Estimated Launch**
GP2015 (Enbrel®)	Pfizer; Amgen	Q4 2018 (50%) or 04/24/29 (50%)
Inflectra™; Remsima® (Remicade®)	Janssen	Q4 2016 (40%) or Q1 2017 (20%) or 09/04/18 (40%)
Neupeg Pegylated Filgrastim™ (Neulasta®)	Amgen	2017 (65%) or 07/29/31 (35%)
Grastofil™ (Neupogen®)	Amgen	2017 (65%) or 07/29/31 (35%)
Retacrit™ (Procrit®)	Amgen; Janssen	Q2 2017 (80%)
Retacrit™ (Epogen®)	Amgen	Q2 2017 (80%)
ABP-501 (Humira)	AbbVie	05/2017 (20%) or 11/2017 (30%) or 08/16/22 (25%) or 07/18/23 (25%)
SB2 (Remicade)	Janssen	Q3 2017 (60%) or 9/4/18 (40%)
CHS-1701 (Neulasta)	Amgen	12/2017 (70%)
LP-EP2006 (Neulasta)	Amgen	1H 2018 (70%) or 07/29/31 (30%)

RESOURCES:

http://www.drugs.com/newdrugs.html

https://www.fdatracker.com/fda-calendar/

http://www.rttnews.com/corpinfo/fdacalendar.aspx

http://www.ipdanalytics.com/

http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/FA25AE/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/56A3BE/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=1034&contentSetId=50&title=INVESTIGATIONAL+DRUGS+-+NEW+DRUG+APPLICATION+%28NDA%29+STATUS&servicesTitle=INVESTIGATIONAL+DRUGS+-+NEW+DRUG+APPLICATION+%28NDA%29+STATUS

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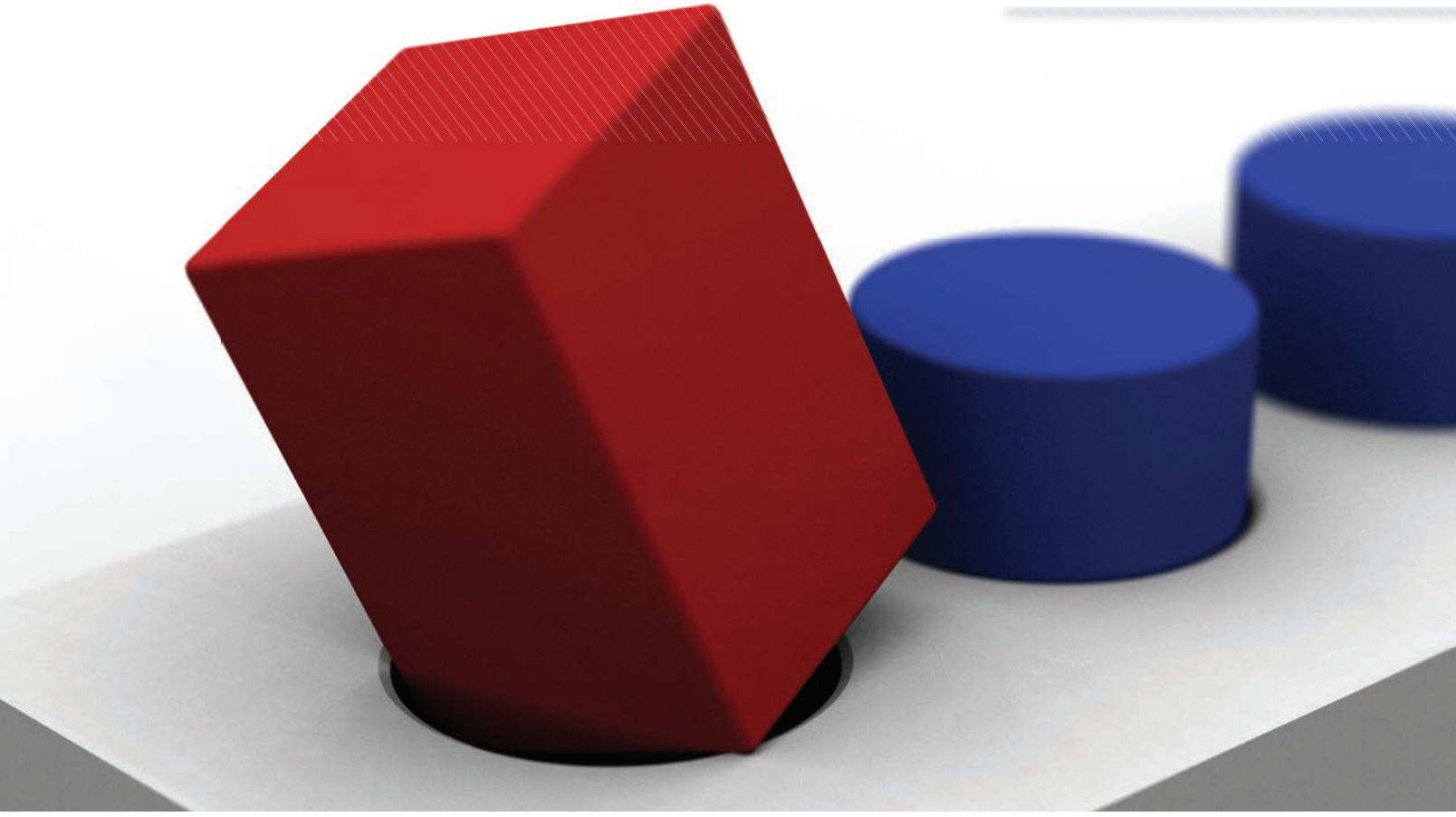

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