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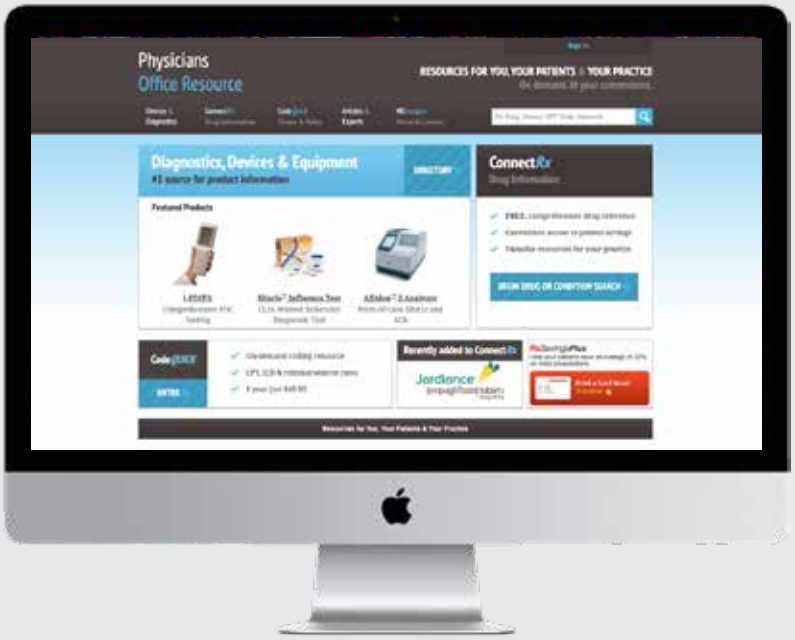
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1. Clinical Laboratory Improvement Amendments (CLIA) / * SEFRIA Fentanyl

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PUBLISHER
Aaron R. Medaris
amedaris@physiciansofficeresource.com

CEO
Andrew C. Nimmo
acnimmo@physiciansofficeresource.com

PRESIDENT
John D. Pasquale
jpasquale@pharmaconnect.com

BUSINESS MANAGER
Marci J. Hills
mhills@physiciansofficeresource.com

TRAVEL EDITOR
Brandi L. Brower

EDITORIAL BOARD
Michael Paquin, FHIMSS
Barry Craig, MLT (NCA), CLC

STAFF WRITER
Dylan J. Chadwick

CREATIVE DIRECTOR
PRODUCTION MANAGER
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TABLE OF CONTENTS



TRANSFORMING MEDICINE WITH AI

Aside from language processing tools like ChatGPT, industries from finance, manufacturing, retail, agriculture, transportation, and entertainment are utilizing AI to do things they have never been able to do before. Take this recent headline: "The Beatles are releasing their 'final' record. AI helped make it possible." Yes, even the Beatles are benefiting from AI technology. With AI transforming industries across the globe, some of the most promising advancements are in the field of healthcare. In this article, we'll look at how AI is transforming medical imaging, precision medicine, drug development and other areas of medicine. **PAGE 6**

22

SCRUBMONEY: FINANCIAL CONSIDERATIONS UNIQUE TO U.S. PHYSICIANS
Simple Steps for Early Action

32

MDecapes: THE SENSEI WAY
Sensei Lana'I, A Four Seasons Resort



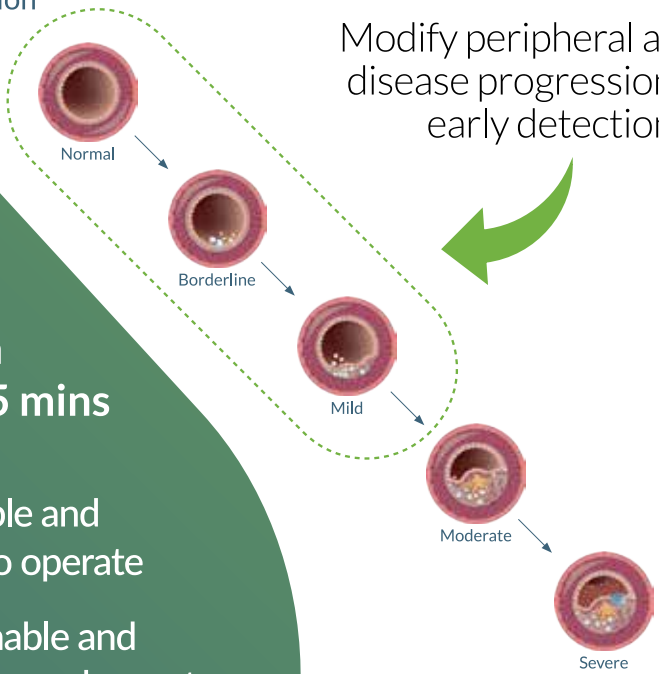
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ML00163.Rev A

*2016 AHA/ACC Lower Extremity PAD Guidelines: Age ≥ 65y; Age 50-64y, with risk factors for atherosclerosis; Age <50 y, with diabetes mellitus; and one additional risk factor or atherosclerosis[1]

1. Gerhard-Herman, M. D., Gornik, H. L., Barrett, C., Barshes, N. R., Corriere, M. A., Drachman, D. E., Fleisher, L. A., Fowkes, F. G., Hamburg, N. M., Kinlay, S., Lookstein, R., Misra, S., Mureebe, L., Olin, J. W., Patel, R. A. G., Regensteiner, J. G., Schanzer, A., Shishehbor, M. H., Stewart, K. J., ... Walsh, M. E. (2017). 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: Executive summary: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. Circulation, 135(12). https://doi.org/10.1161/cir.0000000000000470

2. Thiruvoipati, T., Kielhorn, C. E., & Armstrong, E. J. (2015). Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. World journal of diabetes, 6(7), 961–969. https://doi.org/10.4239/wjd.v6.i7.961


MEDICAL REPORT
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:586 :89 403
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TRANSFORMING MEDICINE WITH AI

BY AARON MEDARIS, PHYSICIANS OFFICE RESOURCE

I think my first true introduction of Artificial Intelligence or AI, (that wasn't from a sci-fi movie) came in February of this year, when I read an article about ChatGPT, a language processing tool that could write essays, papers, and articles in seconds; thus, leading to its quick ban from schools and universities around the nation. Granted it writes articles around a 6th grade level, so if you're using that to cheat your way through college, you probably have other problems coming your way.

Today it seems like every time I open my favorite news app, there's a new article about AI and how it's helping to advance industries across the globe. Aside from language processing tools like ChatGPT, industries from finance, manufacturing, retail, agriculture, transportation, and entertainment are utilizing AI to do things they have never been able to do before. Take this headline from today's news: "The Beatles are releasing their 'final' record. AI helped make it possible." Yes, even the Beatles are benefiting from AI technology.

With AI transforming industries across the globe, some of the most promising advancements are in the field of healthcare. In this article, we'll look at some of the different ways that AI is transforming healthcare.

Medical imaging analysis: AI algorithms can analyze medical images, such as X-rays, CT scans, and MRIs, to detect and diagnose diseases with high accuracy. AI systems can identify patterns and anomalies that may be difficult for human experts to spot, leading to faster and more accurate diagnoses. AI can also provide precise and quantitative measurements from medical images. For example, AI algorithms can calculate tumor size, volume, or growth rates, providing valuable information for treatment planning and monitoring response to therapy. It's also helping to provide image-based risk predictions. By analyzing medical images and patient data, AI algorithms can predict the risk of certain diseases or conditions. For instance, in cardiovascular imaging, AI can analyze cardiac images to assess the risk of future cardiac events and guide preventive measures.

Precision medicine: AI enables personalized treatment plans by analyzing large amounts of patient data, including genetic information, medical records, and lifestyle factors. This data can be used to predict disease risks, identify optimal treatment options, and develop tailored therapies for individual patients. Take for instance, genomic analysis.

AI algorithms can analyze genomic data to identify genetic variations, mutations, and biomarkers associated with specific diseases. By understanding a patient's genetic profile, AI can help determine personalized treatment options and predict disease risks.

Drug discovery and development: AI is being used to accelerate the drug discovery process. AI algorithms can analyze massive datasets to identify potential drug candidates, simulate and predict drug behavior, and optimize drug formulations. This helps in reducing costs and time required for drug development. AI algorithms can even optimize various drug properties, such as efficacy, safety, and pharmacokinetics. By analyzing chemical structures and properties, as well as historical data on drug development, AI can suggest modifications to enhance the potency and selectivity of compounds, improve drug-like properties, and reduce toxicity. One exciting way AI is helping in drug discovery and development is by repurposing existing drugs. AI can identify new therapeutic uses for existing drugs by analyzing large datasets and identifying potential drug-disease associations. By leveraging known drug properties and their effects on different biological pathways, AI algorithms can suggest repurposing strategies, leading to the development of new treatments for different diseases.

Virtual assistants and chatbots: AI-powered virtual assistants and chatbots can interact with patients, answer their questions, and provide basic medical advice. They can triage patients, schedule appointments, and offer information on common symptoms or conditions, improving access to healthcare services and reducing the burden on healthcare providers.

Predictive analytics: AI algorithms can analyze large volumes of patient data to predict disease progression, identify high-risk patients, and optimize treatment plans. This helps healthcare providers make informed decisions and allocate resources more effectively. Take for instance, early disease detection. AI algorithms can analyze patient data, including medical records, genetic information, and lifestyle factors, to identify early indicators of diseases. By detecting patterns and risk factors, AI can predict the likelihood of developing certain conditions, enabling early intervention and preventive measures. AI algorithms can also stratify patients into different risk groups based on their individual characteristics and health data. By considering factors such as age, gender, medical history, genetic markers, and environmental factors, AI can predict the likelihood of adverse events, disease progression, or treatment response. This helps in prioritizing high-risk patients for targeted interventions.

Robot-assisted surgery: AI-enabled robotic systems assist surgeons during complex procedures, providing more precision, flexibility, and control. These systems can enhance surgical outcomes, reduce invasiveness, and shorten recovery times. In fact, AI is helping in robot assisted surgery before the surgery even begins. AI algorithms can assist in preoperative planning by analyzing patient-specific data, including medical images and patient anatomy. By simulating different surgical scenarios, AI can help surgeons visualize the procedure, optimize surgical approaches, and develop personalized surgical plans. During surgery, AI-powered robotic systems can assist surgeons during procedures by performing specific tasks or providing guidance. For example, AI algorithms can enable robotic arms to perform precise suturing or stapling with enhanced stability and dexterity, allowing for more precise tissue manipulation.

Health monitoring and wearable devices: According to a recent survey, about 35 percent of adults use wearable devices. AI algorithms can analyze data from wearable devices, such as fitness trackers and smartwatches, to monitor vital signs, detect abnormalities, and provide real-time feedback on health status. This facilitates remote patient monitoring and early intervention. AI algorithms can analyze wearable data to identify early signs of certain diseases or conditions. By tracking changes in vital signs, sleep patterns, or activity levels, AI can help in early detection and intervention, improving the chances of successful treatment and management.

Patient data management: AI can streamline and improve the management of electronic health records (EHRs). Natural language processing algorithms can extract relevant information from unstructured medical records, improving accuracy and efficiency in data entry and retrieval.

These are just a few examples of how AI is being used in medicine. As the field continues to advance, AI has the potential to revolutionize healthcare delivery, improve patient outcomes, and enhance the overall efficiency of medical systems. But we do need to be careful with our use of AI especially when it comes to our healthcare. An amazing yet concerning fact is that AI is still in its infancy. Think about where we were 30 years ago when America Online was spamming our mailboxes, not inboxes, with CDs of their internet software. Remember the sound of dialup internet via your 56k modem, praying that it would connect long enough and be quick enough so you could check your email? Now think about where we are today in terms of technology. The differences are so great, I don't think many of us in 1996 could even imagine the technological miracles we experience on a daily basis. I personally think we're at the America Online stage of AI, maybe even before that. This is just the beginning, and the advancements are going to come much quicker than they did with the early days of the internet. That's an exciting prospect when you think about it. But I can see why some tech giants and politicians are calling for a pause in AI development while we figure out rules and legislation going forward. AI has already transformed many industries for the better and it has the great potential to change our lives for the better, but if it's not done right, especially with healthcare, it could have the opposite effect. It's my hope that we do get this right and that AI technology continues to advance in a positive way, opening doors to the cure of diseases that have plagued our world for far too long.

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1. Moderately complex on the DCA Vantage Analyzer. CLIA-waived on the CLINITEK Status+ Analyzer.

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From Nova Biomedical

The U.S. FDA has cleared Nova Primary as a blood glucose reference analyzer that fills the need for a new reference analyzer to replace the YSI STAT PLUS 2300 (YSI, Inc., Yellow Springs, OH). Manufacturers of blood glucose measuring devices and clinical diabetes researchers have relied on the YSI 2300 as a reference and correlation analyzer. However, YSI, Inc. no longer supports the analyzer, and its discontinuation has left a critical industry void. With today's FDA clearance, Nova Primary from Nova Biomedical is now available in the U.S. and worldwide.

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2808

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HEMATOLOGY



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- Smart Safety Features

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PERIPHERAL ARTERIAL DISEASE



QUANTAFLO® PAD

From Semler Scientific

QuantaFlo® PAD is an easy to use, accurate, point of care, non-invasive solution that aids in the early detection of peripheral arterial disease (PAD). This FDA cleared device can be administered by a medical aide in less than 5 minutes. As published in the Journal of Vascular Surgery and the American Journal of Preventive Medicine, QuantaFlo detected undiagnosed PAD in 31.6% of patients +65.1 QuantaFlo is portable and integrates with other technologies and platforms. It is ideal for both home and clinic environments.

1. Smolderen KG, Ameli O, Chaisson CE, Heath K, Mena-Hurtado C. Peripheral Artery Disease Screening in the Community and 1-Year Mortality, Cardiovascular Events, and Adverse Limb Events, AJPM Focus (2022), https://doi.org/10.1016/j.focus.2022.100016

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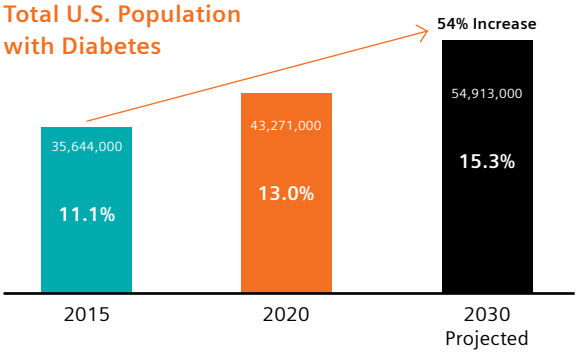


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- Rapid kidney health assessment:
  CLINITEK® Microalbumin 2 Strip
  Albumin-to-creatinine ratio (ACR)





The Prevalence of Diabetes Among U.S. Adults is on the Rise[1]

Help your patients reverse the trend

Customize your patient consultations to enhance physician-patient partnership toward improved outcomes.

siemens-healthineers.us/chronicdisease

1. Rowley, William R et al. "Diabetes 2030: Insights from Yesterday, Today, and Future Trends." Population health management vol. 20,1 (2017): 6-12. doi:10.1089/pop.2015.0181.

SIEMENS Healthineers



NOT JUST ANOTHER ANTIDEPRESSANT

Auvelity is a rapid-acting oral antidepressant with proven efficacy at Week 1*

INDICATION

Auvelity is indicated for the treatment of major depressive disorder (MDD) in adults.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies.**
- **Closely monitor all antidepressant-treated patients for clinical worsening, and emergence of suicidal thoughts and behaviors.**
- **Auvelity is not approved for use in pediatric patients.**

Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages, including **Boxed Warning** for suicidal thoughts and behaviors.



Auvelity™

(dextromethorphan HBr and bupropion HCl)
extended-release tablets 45mg/105mg

Auvelity uses a new approach to treat MDD that is different from other oral antidepressants approved in more than 60 years[1-3†]

Auvelity is the first and only oral NMDA receptor antagonist for MDD[1-3]

Symptom improvement at Week 1 and sustained at Week 6*

- Patients taking Auvelity had significant change from baseline in the MADRS total score at Week 6 vs placebo (primary endpoint: LS mean change of -12.1 vs -15.9; *P*=0.002).[1,4]

Rapid remission starting at Week 2*

- Significantly more patients achieved remission with Auvelity at Week 2 vs placebo (key secondary endpoint: 17% (24/142) vs 8% (12/159); *P*=0.013).[4]

Demonstrated safety profile in controlled and open-label studies*‡

- The most common adverse reactions in a 6-week study (≥5% and >2x placebo) were: dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.[1]
- Long-term safety up to 1 year in an open-label study was consistent with controlled studies.[1,5-7]

Explore the difference at AuvelityHCP.com

Actor Portrayal

*GEMINI Phase 3 study evaluated Auvelity vs placebo in 327 patients (N=163 Auvelity and N=164 placebo) with MDD for 6 weeks. N denotes randomized patients. The mITT population, defined as all randomized patients who took at least 1 dose of study drug and had at least 1 post-baseline assessment, was n=156 Auvelity and n=162 placebo. Key secondary endpoints included change from baseline in MADRS total score at Week 1 (-7.2 Auvelity vs -5.0 placebo; *P*=0.007) and remission (MADRS total score ≤10) at Week 2. The safety population was n=162 Auvelity and n=164 placebo.

†The mechanism of action of Auvelity in the treatment of MDD is unclear.

‡COMET Phase 3 safety study assessed Auvelity up to 1 year in 876 MDD patients (roll-over from prior Auvelity studies and newly enrolled).

LS=least square; MADRS=Montgomery-Åsberg Depression Rating Scale; mITT=modified intent-to-treat; NMDA=N-methyl-D-aspartate

IMPORTANT SAFETY INFORMATION (CONT'D)

CONTRAINDICATIONS

Seizure: Do not use Auvelity in patients with a seizure disorder.

Current or prior diagnosis of bulimia or anorexia nervosa: A higher incidence of seizure was observed in such patients treated with bupropion.

Undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs: Due to risk of seizure.

Monoamine Oxidase Inhibitors (MAOIs): Do not use Auvelity concomitantly with, or within 14 days of stopping, an MAOI due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Conversely, at least 14 days must be allowed after stopping Auvelity before starting an MAOI antidepressant. Do not use Auvelity with reversible MAOIs such as linezolid or intravenous methylene blue.

Hypersensitivity: Do not use in patients with known hypersensitivity to dextromethorphan, bupropion, or any component of Auvelity. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion.

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors in Pediatrics and Young Adults: Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing Auvelity, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Seizure: Bupropion, a component of Auvelity, can cause seizure and the risk is dose related. Because the risk of seizure with bupropion is dose-related, screen patients for use of other bupropion-containing products prior to initiating Auvelity. If concomitant use of Auvelity with other bupropion-containing products is clinically warranted, inform patients of the risk. Discontinue Auvelity and do not restart treatment if the patient experiences a seizure.

Increased Blood Pressure and Hypertension: Treatment with bupropion, a component of Auvelity, can cause elevated blood pressure and hypertension. The risk of hypertension is increased if Auvelity is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity. Assess blood pressure before initiating treatment with Auvelity and monitor periodically during treatment. Monitor blood pressure, particularly in patients who receive the combination of bupropion and are receiving nicotine replacement.

Activation of Mania/Hypomania: Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating Auvelity, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). Auvelity is not approved for use in treating bipolar depression.

Psychosis and Other Neuropsychiatric Reactions: Auvelity contains bupropion and dextromethorphan. Depressed patients treated with bupropion have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Dextromethorphan overdose can cause toxic psychosis, stupor, coma, and hyperexcitability.

Because the risks of neuropsychiatric reactions are dose-related, screen patients for use of other bupropion- or dextromethorphan-containing products prior to initiating Auvelity. If concomitant use of Auvelity with other bupropion- or dextromethorphan-containing products is clinically warranted, monitor patients for neuropsychiatric reactions and instruct patients to contact a healthcare provider if such reactions occur.

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressants, including Auvelity, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including Auvelity, in patients with untreated anatomically narrow angles.

Dizziness: Auvelity may cause dizziness. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that Auvelity therapy does not affect them adversely.

Serotonin Syndrome: Auvelity contains dextromethorphan. Concomitant use with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants increases the risk of serotonin syndrome, a potentially life-threatening condition. Prior to initiating therapy with Auvelity, screen patients for use of other dextromethorphan-containing products. If concomitant use of Auvelity with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome, and monitor for symptoms. Discontinue Auvelity and/or concomitant serotonergic drug(s) immediately if symptoms of serotonin syndrome occur and initiate supportive symptomatic treatment.

WARNINGS AND PRECAUTIONS (CONT'D)

Embryo-fetal Toxicity: Based on animal studies, Auvelity may cause fetal harm when administered during pregnancy. Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

Auvelity™
(dextromethorphan HBr and bupropion HCl)
extended-release tablets 45mg/105mg

DRUG INTERACTIONS

Strong Inhibitors of CYP2D6: Concomitant use with Auvelity increases plasma concentrations of dextromethorphan. Dosage adjustment is necessary. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

Strong CYP2B6 Inducers: Concomitant use with Auvelity decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of Auvelity. Avoid co-administration of Auvelity.

CYP2D6 Substrates: Concomitant use with Auvelity can increase the exposures of drugs that are substrates of CYP2D6. It may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

Digoxin: Concomitant use with Auvelity may decrease plasma digoxin levels. Monitor plasma digoxin levels in patients treated concomitantly with Auvelity.

Drugs that Lower Seizure Threshold: Concomitant use with Auvelity may increase risk of seizure. Use Auvelity with caution. Discontinue Auvelity and do not restart treatment if the patient experiences a seizure.

Dopaminergic Drugs: Concomitant use with Auvelity can result in central nervous system toxicity. Use Auvelity with caution.

USE IN SPECIFIC POPULATIONS

Lactation: Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with Auvelity and for 5 days following final dose.

Renal Impairment: Dosage adjustment is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2). Auvelity is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

Hepatic Impairment: Auvelity is not recommended in patients with severe hepatic impairment.

ADVERSE REACTIONS

Most common adverse reactions (≥5% and twice the rate of placebo): dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).

Please see Brief Summary of Prescribing Information on the following pages, including Boxed Warning for suicidal thoughts and behaviors.

AUV HCP ISI 08/2022

References: 1. Auvelity [Prescribing Information]. Axsome Therapeutics, Inc.: New York, NY **2.** Thomas D, and Wessel C. The state of innovation in highly prevalent chronic diseases volume I: Depression therapeutics. December 2017. https://www.bio.org/sites/default/files/legacy/bioorg/docs/BIO_HPCD_Series-Depression_2018-01-03.pdf. Accessed March 21, 2022. **3.** FDA Depression Medicines. https://www.fda.gov/media/132665/download. Accessed March 21, 2022. **4.** Iosifescu DV, Jones A, O'Gorman C, et al. Efficacy and safety of AXS-05 (dextromethorphan-bupropion) in patients with major depressive disorder: A phase 3 randomized clinical trial (GEMINI). *J Clin Psychiatry*. 2022;83(4):21m14345. **5.** Data on File. AXS0080921. **6.** Tabuteau H, Jones A, Anderson A, et al. Effect of AXS-05 (dextromethorphan-bupropion) in major depressive disorder: A randomized double-blind controlled trial. *Am J Psychiatry*. 2022;179(7):490-499. **7.** Data on File. AXS0060921.

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Actor Portrayal

AUVELITY™ (dextromethorphan Hbr-bupropion HCl) extended-release tablets, for oral use

Brief Summary of Prescribing Information

BEFORE PRESCRIBING AUVELITY, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Antidepressants increased risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies.**
- **Closely monitor all antidepressant-treated patients for clinical worsening, and emergence of suicidal thoughts and behaviors.**
- **AUVELITY is not approved for use in pediatric patients.**

INDICATIONS AND USAGE

AUVELITY is indicated for the treatment of major depressive disorder (MDD) in adults.

CONTRAINDICATIONS

AUVELITY is contraindicated in patients:

- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate release formulation of bupropion
- undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
- taking, or within 14 days of stopping, MAOIs due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Starting AUVELITY in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated.
- with known hypersensitivity to bupropion, dextromethorphan, or other components of AUVELITY. Anaphylactoid / anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion.

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18-24 years old	5 additional patients
	Decreases Compared to Placebo
25-64 years old	1 fewer patient
≥65 years old	6 fewer patients

*AUVELITY is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing AUVELITY, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Seizure

Bupropion, a component of AUVELITY, can cause seizure. The risk of seizure with bupropion is dose-related.

When a bupropion hydrochloride (HCl) sustained-release tablet was dosed up to 300 mg per day (approximately 1.5 times the maximum recommended daily dosage of AUVELITY), the incidence of seizure was approximately 0.1% (1/1,000) and increased to approximately 0.4% (4/1,000) at the maximum recommended dosage for the sustained-release tablet of 400 mg per day (approximately 2 times the maximum recommended daily dosage of AUVELITY).

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with AUVELITY. AUVELITY is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs. The following conditions can also increase the risk of seizure: severe head injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids); metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); use of illicit drugs (e.g., cocaine); or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

Because the risk of seizure with bupropion is dose-related, screen patients for use of other bupropion-containing products prior to initiating AUVELITY. If concomitant use of AUVELITY with other bupropion-containing products is clinically warranted, inform patients of the risk. Discontinue AUVELITY and do not restart treatment if the patient experiences a seizure.

Increased Blood Pressure and Hypertension

AUVELITY contains bupropion, which can cause elevated blood pressure and hypertension. The risk of hypertension is increased if AUVELITY is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity. Assess blood pressure prior to initiating treatment, and periodically monitor blood pressure during treatment with AUVELITY.

Activation of Mania/Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating AUVELITY, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). AUVELITY is not approved for use in treating bipolar depression.

Psychosis and Other Neuropsychiatric Reactions

AUVELITY contains bupropion and dextromethorphan. Depressed patients treated with bupropion have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Dextromethorphan overdose can cause toxic psychosis, stupor, coma, and hyperexcitability.

Because the risks of neuropsychiatric reactions are dose-related, screen patients for use of other bupropion- or dextromethorphan-containing products prior to initiating AUVELITY. If concomitant use of AUVELITY with other bupropion- or dextromethorphan-containing products is clinically warranted, monitor patients for neuropsychiatric reactions and instruct patients to contact a healthcare provider if such reactions occur.

Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including bupropion, a component of AUVELITY, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including AUVELITY, in patients with untreated anatomically narrow angles.

Dizziness

AUVELITY may cause dizziness. In controlled studies of AUVELITY, 14% of patients receiving AUVELITY and 6% of patients on placebo experienced dizziness. Take precautions to reduce the risk of falls, particularly for patients with motor impairment affecting gait or those with a history of falls. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that AUVELITY therapy does not affect them adversely.

Serotonin Syndrome

AUVELITY contains dextromethorphan. Concomitant use of AUVELITY with SSRIs or tricyclic antidepressants may cause serotonin syndrome, a potentially life-threatening condition with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor.

Prior to initiating AUVELITY, screen patients for use of other dextromethorphan-containing products. If concomitant use of AUVELITY with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms. Discontinue AUVELITY and/or concomitant serotonergic drug(s) immediately if the above symptoms occur and initiate supportive symptomatic treatment.

Embryo-fetal Toxicity

Based on animal studies, AUVELITY may cause fetal harm when administered during pregnancy. In developmental toxicity studies in rats and rabbits, when a combination of dextromethorphan/quinidine was given to pregnant animals, fetal malformations (rabbits) and embryolethality were demonstrated in offspring. Neurotoxicity findings were observed in juvenile rats treated with a combination of dextromethorphan/quinidine on postnatal day (PND) 7, which corresponds to the third trimester of gestation through the first few months of life and may extend through the first three years of life in humans. The separate effect of dextromethorphan on developmental toxicity at the recommended clinical dose is unclear. Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

ADVERSE REACTIONS

Clinical Trials Experience

AUVELITY was evaluated for safety in a total of 1114 patients with MDD or another indication from four studies (two 6-week studies in MDD, one 6-week study in another indication, and one long-term study in MDD and another indication). One 6-week study in MDD employed placebo as a control arm. Two 6-week studies, one in MDD and one in another indication, employed bupropion as a control arm. In the patients treated with AUVELITY in the long-term study (n=876), 597 received at least 6 months of treatment, and 110 received at least 12 months of treatment. The data below are based on the 6-week, placebo-controlled study in which either AUVELITY (n=162) or placebo (n=164) was administered twice daily to patients with MDD (Study 1).

Adverse Reactions Leading to Discontinuation
In the 6-week placebo-controlled study, 4% of patients treated with AUVELITY and 0% of placebo-treated patients discontinued participation due to adverse reactions. The adverse reaction that led to study discontinuation in ≥1% of patients treated with AUVELITY was anxiety (2%).

Most Common Adverse Reactions
In the 6-week placebo-controlled clinical study, the most common (incidence ≥5% for AUVELITY and more than twice as frequently as placebo) adverse reactions were dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).

Table 2: Adverse Reactions Occurring in ≥ 2% of Adult Patients with MDD Treated with AUVELITY and More Frequently than in Patients Treated with Placebo in a 6-Week Placebo-Controlled Study (Study 1)

Adverse Reaction	AUVELITY (N=162) %	Placebo (N=164) %
Dizziness	16	6
Nausea	13	9
Headache	8	4
Diarrhea	7	3
Somnolence	7	3
Dry mouth	6	2
Sexual dysfunction[a]	6	0
Hyperhidrosis	5	0
Anxiety	4	1
Constipation	4	2
Decreased appetite	4	1
Insomnia	4	2
Arthralgia	3	0
Fatigue[b]	3	2
Paraesthesia[c]	3	0
Vision blurred	3	0

[a]Sexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia
[b]Fatigue includes fatigue, lethargy
[c]Paraesthesia includes paraesthesia, hypoaesthesia

DRUG INTERACTIONS

Table 3: Clinically Important Drug Interactions with AUVELITY

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	The concomitant use of AUVELITY with MAOIs increases the risk of hypertensive crisis and serotonin syndrome.
Intervention	AUVELITY is contraindicated in patients taking MAOIs (including MAOIs such as linezolid or intravenous methylene blue) or in patients who have taken MAOIs within the preceding 14 days. Allow at least 14 days after stopping AUVELITY before starting an MAOI.
Serotonergic Drugs	
Clinical Impact	Concomitant use of AUVELITY with other serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Monitor for symptoms of serotonin syndrome when AUVELITY is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of AUVELITY and/or concomitant serotonergic drugs.
Drugs that Lower Seizure Threshold	
Clinical Impact	AUVELITY contains bupropion which can cause seizure. Co-administration with other drugs that lower seizure threshold may increase risk of seizure.
Intervention	Use caution when administering AUVELITY concomitantly with drugs that lower the seizure threshold. Discontinue AUVELITY and do not restart treatment if the patient experiences a seizure.
Strong Inhibitors of CYP2D6	
Clinical Impact	Concomitant use of AUVELITY with strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan.
Intervention	Dosage adjustment is necessary when AUVELITY is coadministered with strong inhibitors of CYP2D6. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.
Strong Inducers of CYP2B6	
Clinical Impact	Concomitant use of AUVELITY with strong CYP2B6 inducers decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of AUVELITY.
Intervention	Avoid co-administration of AUVELITY with strong inducers of CYP2B6. Consider alternatives to strong CYP2B6 inducers if needed.
Drugs Metabolized by CYP2D6	
Clinical Impact	*CYP2D6 Substrates* Coadministration of AUVELITY with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. *Drugs that Require Metabolic Activation by CYP2D6* Drugs that require metabolic activation by CYP2D6 to be effective could have reduced efficacy when administered concomitantly with AUVELITY.
Intervention	*CYP2D6 Substrates* When used concomitantly with AUVELITY, it may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index. *Drugs that Require Metabolic Activation by CYP2D6* Patients treated concomitantly with AUVELITY may require increased doses of drugs that require activation by CYP2D6 to be effective.
Digoxin	
Clinical Impact	Coadministration of AUVELITY with digoxin may decrease plasma digoxin levels.
Intervention	Monitor plasma digoxin levels in patients treated concomitantly with AUVELITY and digoxin.
Dopaminergic Drugs	
Clinical Impact	CNS toxicity was reported when bupropion was co-administered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness.
Intervention	Use caution when administering AUVELITY concomitantly with dopaminergic drugs.
Alcohol	
Clinical Impact	AUVELITY contains bupropion which can increase adverse neuropsychiatric events or reduce alcohol tolerance.
Intervention	The consumption of alcohol should be minimized or avoided during treatment with AUVELITY.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including AUVELITY, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or online at: https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/

Risk Summary
Based on animal studies, AUVELITY may cause fetal harm when administered during pregnancy. AUVELITY is not recommended during pregnancy. If a female becomes pregnant while being treated with AUVELITY, discontinue treatment and counsel the patient about the potential risk to a fetus.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks to the mother of untreated depression and potential effects on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Lactation

Risk Summary
Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with AUVELITY and for 5 days following final dose.

Renal Impairment

Dosage adjustment of AUVELITY is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2). The pharmacokinetics of AUVELITY have not been evaluated in patients with severe renal impairment. AUVELITY is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

Hepatic Impairment

No dose adjustment of AUVELITY is recommended in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of AUVELITY have not been evaluated in patients with severe hepatic impairment (Child-Pugh C). AUVELITY is not recommended in patients with severe hepatic impairment.

CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher dextromethorphan concentrations than extensive/intermediate CYP2D6 metabolizers.

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FEDERAL

FINANCIAL CONSIDERATIONS UNIQUE TO U.S. PHYSICIANS

Simple Steps for Early Action

BY ANDREW HARMS AND MIRIAM SWEENEY

For the average U.S. household, everyday living is getting pricey. Childcare, food, energy, transportation, and housing costs are all rising. Among U.S. physicians and healthcare professionals, personal financial matters may make things tougher given high educational debt-loads, capped income levels during residency years, and unique insurance needs. Furthermore, job-related stressors emanating from clinical and patient-care priorities, administrative duties, continuing education, licensing requirements, and professional responsibilities leave little time for prudent, active personal financial management.

Self-reported depression and burnout rates are high. In fact, in recent years more than 4 in 10 U.S. physicians report feeling burned out. When asked to rate factors that contribute to depression, results from Medscape's annual National Physician Lifestyle Report indicate personal finances ranked second to job/workplace as a contributing factor.

When asked what would reduce their burnout, the number one response from physicians (roughly a third) indicated the best way to combat burnout would be increased financial compensation. We want to be paid more. In fact, more money was a more common response than a more manageable schedule.

The circumstances facing a physician's personal finances present a unique challenge to most in medicine, regardless of specialty. A predominant factor to financial troubles for physicians includes the high cost of education required to become a physician.

According to the AMA, one in four medical students graduates with training-related debt that exceeds $200,000, and half of medical school graduates report debt burdens greater than $150,000. Those financial burdens are combined with a demanding schedule during graduate medical education and can affect well-being for physician residents and fellows. "Between financial restraints and 80-hour workweeks, trainees often struggle with having the time and budget for necessities. When residency and fellowship programs provide benefits to assist with these needs, it can significantly improve trainee well-being," said AMA Trustee Jesse Ehrenfeld, MD, MPH.

Compounding the difficulties, we recognize that the time and attention required to study medicine, biological sciences, and patient care during training to become a physician leaves little room to acquire a solid education in personal financial management.

Prioritizing personal financial literacy for early-career physicians

Many physicians have access to financial resources early on in their career, but that doesn't mean they're confident about their financial situation. At the medical school level, some hopeful trends have emerged to address the rising educational debt levels burdening many graduates.

At a handful of US medical schools, financial aid offices have transitioned to financial wellness offices—aiming to better help students with personal financial understanding, housing and living expense considerations, etc.—moving beyond simply providing tuition financing guidance in order to provide holistic financial support and literacy. A great example of this is witnessed at the University of Arkansas for Medical Sciences, where Jason Mizell, M.D., and UAMS faculty have facilitated a popular 'Business of Medicine' course since 2012, taught to residents and fourth-year medical students. This course serves to teach early-stage physicians both practice management finance (coding, billing, malpractice, etc.) and, very importantly, personal finance.

Another excellent example of an offering available to medical students is provided by the University of Wisconsin School of Medicine and Public Health. When medical student Rufus Sweeney struck up conversations with his peers some years ago about their personal finances, he was shocked by how few understood their student debt or even knew about options to pay it off. With a grant from the Wisconsin Medical Society, Rufus joined with Emma Crawford, UW SMPH Director of Financial Wellness and Financial Aid Advising, to develop UW-Madison SMPH's first ever course focused on physician personal finance. This course continues and remains the most popular elective credit offering at the medical school.

While such personal finance educational initiatives exemplified by UAMS and UW-Madison go a long way to improving financial literacy for young physicians, the trend to educate and empower physicians in the way of personal finances should be prioritized in order to meet cost of living challenges and resultant burnout rates. An introduction to personal finance is a great offering at the medical school level, and—if followed on with subsequent support at each next stage of a physician's career—would provide a proper runway to financial health and wellness.

At the residency level, new expenditure considerations often outweigh the long-awaited first paycheck. Many times, newly minted residents find themselves unprepared to manage a tight budget. A resident may sometimes find financial resources made available as a new employee helpful—though the quality and availability of personal financial support is disparate and often inadequate. While the financial picture of a resident includes income, the AMA clearly points out the following: "It takes years to realize your earning potential. As a physician, you will not maximize your earnings until the completion of your graduate medical education. The average first-year resident makes around $60,000, (2018 report) and there's not much wiggle room. Resident salaries are determined by an institution and correlate with training year rather than specialty. So, in a given training institution, all residents who are in their third year of training get the same salary, and all in their sixth year are paid the same."

Given the ceiling on income, how many physicians at the resident level have developed the experience and skills to single handedly manage the new challenges to their budget which may stem from debt-repayment, insurance needs, retirement saving, and other important considerations?

Factoring in time constraints and the reasonable desire for a personal life, very few residents have the time to dedicate to getting a handle on personal finances. A host of negative consequences may arise if physicians make financial mistakes at these early stages.

Where to start? Where to turn for help? Start simply.

Financial health should be treated in a similar way to attending to physical and mental health. When viewed from this perspective, the training of physicians gives this occupational group an advantage when tackling personal finances.

Let's outline some simple steps early-career physicians can take to prepare for a healthier financial future:

BECOME FAMILIAR WITH YOUR FINANCIAL VITAL SIGNS:

While carving out time from a busy schedule may seem impossible, scheduling a bit of time to learn some basics about your individual circumstances is essential. Dedicate some time—think about this as you would think about making an appointment with a doctor. Put it on your calendar.

BEGIN WITH SOME BASIC INFORMATION GATHERING

Identify all sources of household income (review your paychecks, line by line); identify your fixed monthly expenses (housing payments, childcare costs, set-aside contributions for savings, etc.), as well as your variable monthly expenses (utilities, subscription services, transportation costs, etc.). As in most things in life, the best first step is figuring out where you are.

CONSTRUCT A MONTHLY BUDGET

You may think of this step as you would a treatment regimen. Crafting a monthly financial plan that identifies each incoming dollar and prudently purposes each outgoing dollar will provide a way forward and likely reduce the mental burden of financial unknowns. There are many good budgeting templates and guides. Like finding a good primary care physician, find yourself a budget that you like and works well for you. And like any treatment regimen, stick to your budget in order to achieve good health.

KNOW YOUR DEBT REPAYMENT OPTIONS

For the majority of physicians, this step is vital to understand and implement. One resource worth checking out is provided by Doctored Money, a non-profit serving physicians that has wonderful debt repayment tools and calculators.

IDENTIFY SUPPORT AND ESTABLISH COMMUNICATION

Assess your surroundings to locate trustworthy financial resources and fiduciary support, if needed. In many cases, the institution with which you are affiliated may have personal financial resources offered. Take advantage of these opportunities when available, if nothing else than to better educate yourself. Once you've built a network of professionals with whom you can confide, communicate to them as you would with your PCP, remembering that your goal is to limit risks and improve your overall health.

CONDUCT ROUTINE FINANCIAL CHECK-UPS

Living within a smartly formulated monthly budget is a winning health strategy, and combined with periodic (quarterly, semi-annual, annual) reviews of your financial vitals will increase your ability to achieve your financial goals. Schedule these reviews on your calendar well in advance, and approach them as you would a visit to any healthcare specialist. Satisfied debts, cost of living adjustments, salary increases, unexpected expenses, changes in the investable landscape, and other life events will prompt adjustments to your monthly budget. Regular check-ups will help you recognize and appropriately transition your personal finances. Utilize your network of resources and professional support on a regularly scheduled basis.

We've been talking a lot about early-career physician groups, but our suggestions are applicable to most, if not all, readers.

Address your financial needs with consistency, and in spite of uncertainties facing the cost of goods and households, we'll make the U.S. healthcare system a secure, confident foundation for personal and community growth.

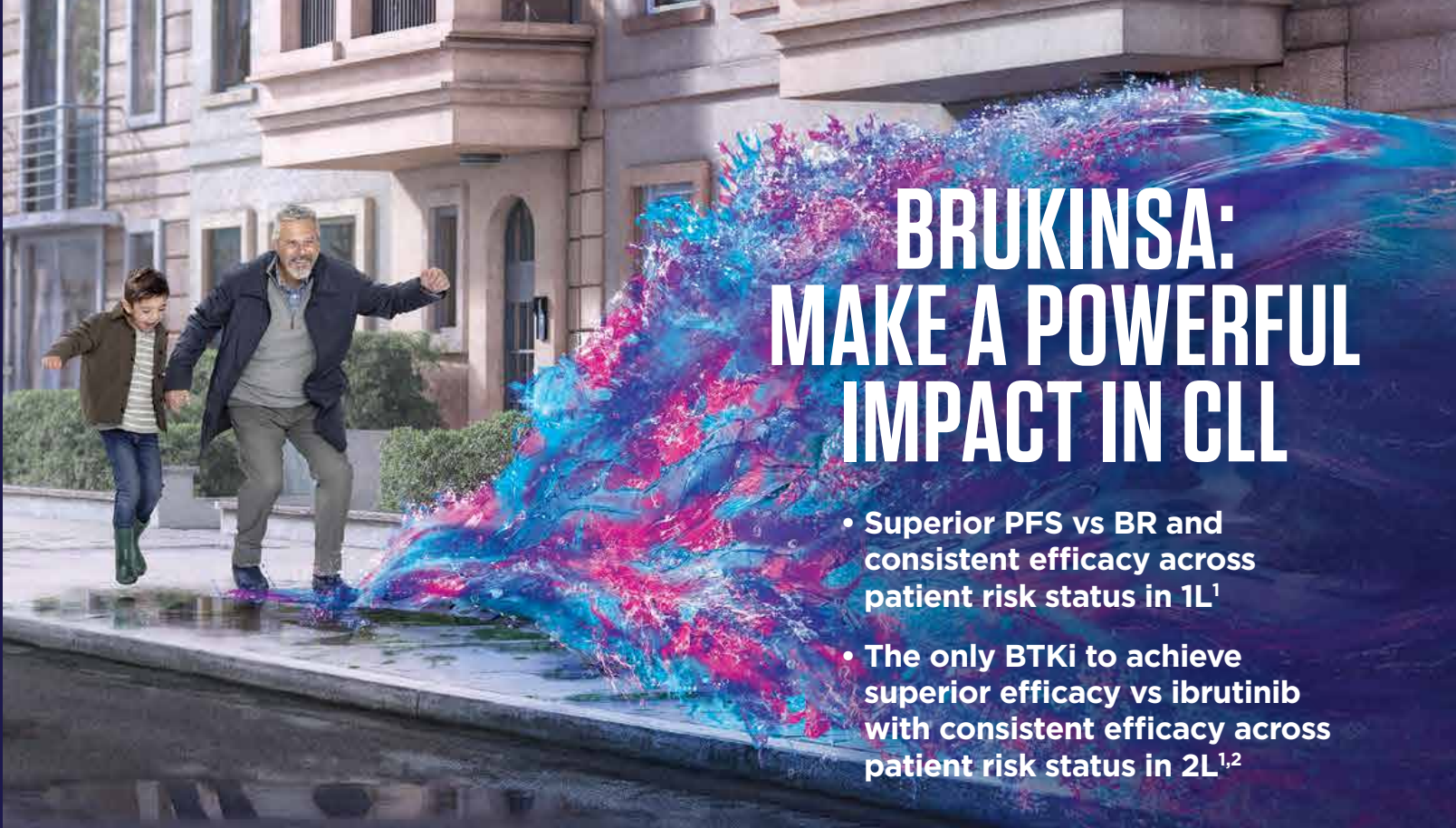
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BRUKINSA: MAKE A POWERFUL IMPACT IN CLL

- **Superior PFS vs BR and consistent efficacy across patient risk status in 1L[1]**
- **The only BTKi to achieve superior efficacy vs ibrutinib with consistent efficacy across patient risk status in 2L[1,2]**

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage
Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage, including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections
Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%) and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

Second Primary Malignancies
Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias
Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately, and consider the risks and benefits of continued BRUKINSA treatment.

Embryo-Fetal Toxicity
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥30% of patients who received BRUKINSA (N=1550) included decreased neutrophil count (42%), upper respiratory tract infection (39%), decreased platelet count (34%), hemorrhage (30%), and musculoskeletal pain (30%).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

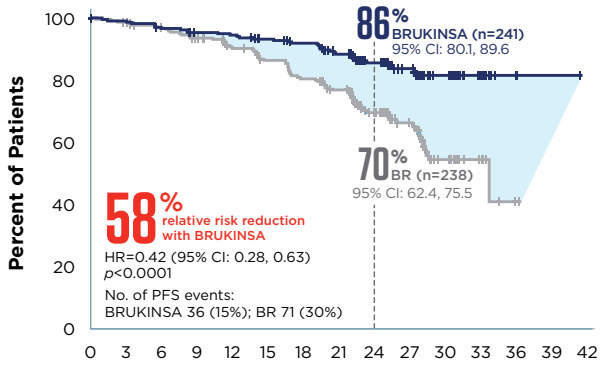
Please see Brief Summary of full Prescribing Information on the following pages.

1L=first line; 2L=second line; BR=bendamustine+rituximab; BTKi=Bruton's tyrosine kinase inhibitor; CI=confidence interval; CLL=chronic lymphocytic leukemia; HR=hazard ratio; IRC=independent review committee; ORR=overall response rate; PFS=progression-free survival; SLL=small lymphocytic lymphoma.

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1L SUPERIORITY: SEQUOIA STUDY

Superior PFS vs BR: patients without del(17p)*[1,3]
(primary endpoint)

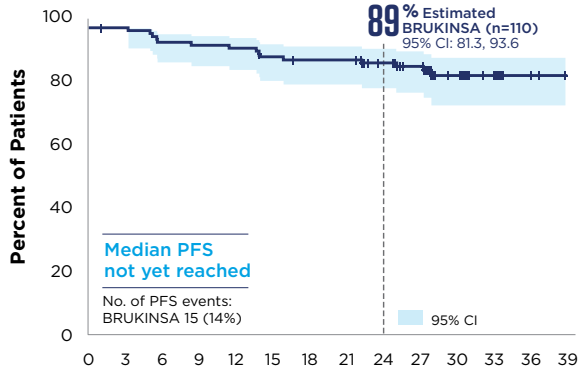


Median follow-up: 26.2 months

No. of patients at risk

BRUKINSA	241	237	230	224	222	214	208	195	123	79	31	17	2	1	0
BR	238	218	210	200	187	176	164	150	89	54	20	8	1	0	

Consistent PFS in del(17p) patients: similar benefit to patients without del(17p)*[3]
(secondary endpoint)



Median follow-up: 30.5 months

No. of patients at risk

BRUKINSA	110	109	104	103	102	98	96	96	86	74	37	19	2	0

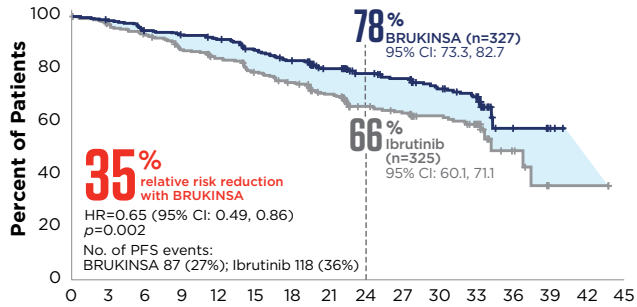
The largest prospective study of 1L patients with del(17p)

*Prespecified analysis assessed by IRC.

SEQUOIA was a global Phase 3 trial evaluating BRUKINSA vs BR in 479 patients with previously untreated CLL/SLL without del(17p). 110 patients with del(17p) were evaluated in a separate single-arm cohort and received BRUKINSA only. Statistical analysis for PFS in the BRUKINSA arm and the BR arm was conducted at a minimum 2-sided alpha of 0.05 for superiority.[1,3]

2L SUPERIORITY: ALPINE STUDY

Superior PFS vs ibrutinib: all-comer population†[2]
(secondary endpoint)

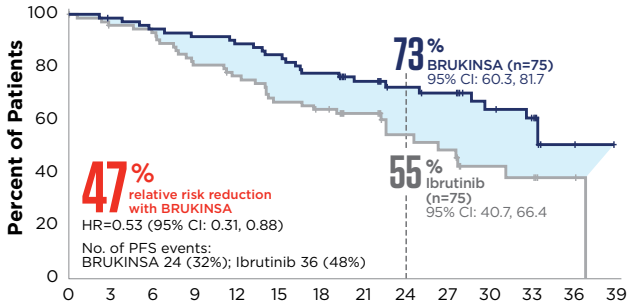


Median follow-up: 29.6 months

No. of patients at risk

BRUKINSA	327	316	303	297	290	274	260	221	165	158	122	111	12	2	0
Ibrutinib	325	306	293	273	259	241	227	186	128	121	97	87	9	1	1	0

Consistent PFS in del(17p) patients: similar benefit to all-comer population†[2]
(prespecified exploratory analysis)



Median follow-up: 29.6 months

No. of patients at risk

BRUKINSA	75	71	68	66	64	61	56	47	32	30	21	18	3	0
Ibrutinib	75	70	68	59	55	48	45	34	19	17	10	9	2	0

Superior ORR (primary endpoint): **80% with BRUKINSA** (95% CI: 76.0, 85.0) **vs** **73% with ibrutinib** (95% CI: 68.0, 78.0) (Median follow-up: 24.7 months; *p*=0.0264)†[1,2]

Data presented are consistent with label.[4]

†Assessed by both IRC and investigator with similar results.

ALPINE was a global Phase 3 trial evaluating BRUKINSA vs ibrutinib in 652 patients with relapsed/refractory CLL/SLL. Statistical analysis for PFS and ORR were initially conducted for noninferiority. When noninferiority was met, superiority was tested.[1,2]

References: 1. BRUKINSA. Package insert. BeiGene, Ltd; 2023. **2.** Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(4):319-332. **3.** Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2022;23(8):1031-1043. **4.** *Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers: Guidance for Industry*. US Department of Health and Human Services, Food and Drug Administration; 2018. Accessed December 20, 2022. https://www.fda.gov/media/102575/download

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
FOR BRUKINSA® (zanubrutinib)
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Waldenström's Macroglobulinemia

BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.2)]*.

1.3 Marginal Zone Lymphoma

BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti–CD20-based regimen.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.4 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

BRUKINSA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.4)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre and post surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%), and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.4)]*. Treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately *[see Dosage and Administration (2.4)]*, and consider the risks and benefits of continued BRUKINSA treatment.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5)]*

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 data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single-agent in nine clinical trials, administered at 160 mg twice daily in 1445 patients and at 320 mg once daily in 105 patients. Among these 1550 patients, the median duration of exposure was 26 months, 80% of patients were exposed for at least 12 months, and 58% of patients were exposed for at least 24 months.

In this pooled safety population, the most common adverse reactions (≥30%), including laboratory abnormalities, included neutrophil count decreased (42%), upper respiratory tract infection (39%), platelet count decreased (34%), hemorrhage (30%), and musculoskeletal pain (30%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] *[see Clinical Studies (14.1)]*. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count ≥75 x 10^9/L and an absolute neutrophil count ≥1 x 10^9/L independent of growth factor support, hepatic enzymes ≤2.5 x upper limit of normal, total bilirubin ≤1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥50 x 10^9/L and an absolute neutrophil count ≥1 x 10^9/L independent of growth factor support, hepatic enzymes ≤3 x upper limit of normal, total bilirubin ≤1.5 x ULN. Both trials required a CLcr ≥30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection, and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer, and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Infections and infestations	Upper respiratory tract infection[a]	39	0
	Pneumonia[b]	15	10[c]
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rash[d]	36	0
	Bruising[e]	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage[f]	11	3.4[c]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[g]	14	3.4
Respiratory, thoracic and mediastinal disorders	Cough	12	0

[a] Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral.
[b] Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral.
[c] Includes fatal adverse reaction.
[d] Rash includes all related terms containing rash.
[e] Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.
[f] Hemorrhage includes all related terms containing hemorrhage, hematoma.
[g] Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.

Other clinically significant adverse reactions that occurred in <10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), and headache (4.2%).

Table 4: Selected Laboratory Abnormalities[a] (>20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Patients (N=118)	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	45	20
Lymphocytosis[b]	41	16
Platelets decreased	40	7
Hemoglobin decreased	27	6
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

[a] Based on laboratory measurements.
[b] Asymptomatic lymphocytosis is a known effect of BTK inhibition.

Waldenström's Macroglobulinemia (WM)

The safety of BRUKINSA was investigated in two cohorts of Study BGB-3111-302 (ASPEN). Cohort 1 included 199 patients with MYD88 mutation (*MYD88^{MUT}*) WM, randomized to and treated with either BRUKINSA (101 patients) or ibrutinib (98 patients). The trial also included a non-randomized arm, Cohort 2, with 26 wild type MYD88 (*MYD88^{WT}*) WM patients and 2 patients with unknown MYD88 status *[see Clinical Studies (14.2)]*.

Among patients who received BRUKINSA, 93% were exposed for 6 months or longer, and 89% were exposed for greater than 1 year.

In Cohort 1 of the ASPEN study safety population (N=101), the median age of patients who received BRUKINSA was 70 years (45-87 years old); 67% were male, 86% were White, 4% were Asian and 10% were not reported (unknown race). In Cohort 2 of the ASPEN study safety population (N=28), the median age of patients who received BRUKINSA was 72 (39-87 years old); 50% were male, 96% were White and 4% were not reported (unknown race).

In Cohort 1, serious adverse reactions occurred in 44% of patients who received BRUKINSA. Serious adverse reactions in >2% of patients included influenza (3%), pneumonia (4%), neutropenia and neutrophil count decreased (3%), hemorrhage (4%), pyrexia (3%), and febrile neutropenia (3%). In Cohort 2, serious adverse reactions occurred in 39% of patients. Serious adverse reactions in >2 patients included pneumonia (14%).

Permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 2% of patients in Cohort 1 and included hemorrhage (1 patient), neutropenia and neutrophil count decreased (1 patient); in Cohort 2, permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 7% of patients and included subdural hemorrhage (1 patient) and diarrhea (1 patient).

Dosage interruptions of BRUKINSA due to an adverse reaction occurred in 32% of patients in Cohort 1 and in 29% in Cohort 2. Adverse reactions which required dosage interruption in >2% of patients included neutropenia, vomiting, hemorrhage, thrombocytopenia, and pneumonia in Cohort 1. Adverse reactions leading to dosage interruption in >2 patients in Cohort 2 included pneumonia and pyrexia.

Dose reductions of BRUKINSA due to an adverse reaction occurred in 11% of patients in Cohort 1 and in 7% in Cohort 2. Adverse reactions which required dose reductions in >2% of patients included neutropenia in Cohort 1. Adverse reaction leading to dose reduction occurred in 2 patients in Cohort 2 (each with one event: diarrhea and pneumonia).

Table 5 summarizes the adverse reactions in Cohort 1 in ASPEN.

Table 5: Adverse Reactions (≥10%) Occurring in Patients with WM Who Received BRUKINSA in Cohort 1

Body System	Adverse Reaction	BRUKINSA (N=101)		Ibrutinib (N=98)	
		All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection[a]	44	0	40	2
	Pneumonia[b]	12	4	26	10
	Urinary tract infection	11	0	13	2
Gastrointestinal disorders	Diarrhea	22	3	34	2
	Nausea	18	0	13	1
	Constipation	16	0	7	0
	Vomiting	12	0	14	1
General disorders	Fatigue[c]	31	1	25	1
	Pyrexia	16	4	13	2
	Edema peripheral	12	0	20	0
Skin and subcutaneous tissue disorders	Bruising[d]	20	0	34	0
	Rash[e]	29	0	32	0
	Pruritus	11	1	6	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[f]	45	9	39	1
	Muscle spasms	10	0	28	1
Nervous system disorders	Headache	18	1	14	1
	Dizziness	13	1	12	0
Respiratory, thoracic and mediastinal disorders	Cough	16	0	18	0
	Dyspnea	14	0	7	0
Vascular disorders	Hemorrhage[g]	42	4	43	9
	Hypertension	14	9	19	14

[a] Upper respiratory tract infection includes upper respiratory tract infection, laryngitis, nasopharyngitis, sinusitis, rhinitis, viral upper respiratory tract infection, pharyngitis, rhinovirus infection, upper respiratory tract congestion.
[b] Pneumonia includes lower respiratory tract infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia viral.
[c] Fatigue includes asthenia, fatigue, lethargy.
[d] Bruising includes all related terms containing bruise, contusion, or ecchymosis.
[e] Rash includes all related terms rash, maculo-papular rash, erythema, rash erythematous, drug eruption, dermatitis allergic, dermatitis atopic, rash pruritic, dermatitis, photodermatoses, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, skin toxicity.
[f] Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, bone pain, spinal pain, musculoskeletal chest pain, neck pain, arthritis, musculoskeletal discomfort.
[g] Hemorrhage includes epistaxis, hematuria, conjunctival hemorrhage, hematoma, rectal hemorrhage, periorbital hemorrhage, mouth hemorrhage, post procedural hemorrhage, hemoptysis, skin hemorrhage, hemorrhoidal hemorrhage, ear hemorrhage, eye hemorrhage, hemorrhagic diathesis, periorbital hematoma, subdural hemorrhage, wound hemorrhage, gastric hemorrhage, lower gastrointestinal hemorrhage, spontaneous hematoma, traumatic hematoma, traumatic intracranial hemorrhage, tumor hemorrhage, retinal hemorrhage, hematochezia, diarrhea hemorrhagic, hemorrhage, melena, post-procedural hematoma, subdural hematoma, anal hemorrhage, hemorrhagic disorder, pericardial hemorrhage, postmenopausal hemorrhage, stoma site hemorrhage, subarachnoid hemorrhage.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included localized infection, atrial fibrillation or atrial flutter, and hematuria.

Table 6 summarizes the laboratory abnormalities in ASPEN.

Table 6: Select Laboratory Abnormalities[a] (≥20%) that Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	BRUKINSA[b]		Ibrutinib[b]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	50	24	34	9
Platelets decreased	35	8	39	5
Hemoglobin decreased	20	7	20	7
Chemistry abnormalities				
Glucose increased	45	2.3	33	2.3
Creatinine increased	31	1	21	1
Calcium decreased	27	2	26	0
Potassium increased	24	2	12	0
Phosphate decreased	20	3.1	18	0
Urate increased	16	3.2	34	6
Bilirubin increased	12	1	33	1

[a] Based on laboratory measurements.
[b] The denominator used to calculate the rate varied from 86 to 101 based on the number of patients with a baseline value and at least one post-treatment value.

Marginal Zone Lymphoma

The safety of BRUKINSA was evaluated in 88 patients with previously treated MZL in two single-arm clinical studies, BGB-3111-214 and BGB-3111-AU-003 *[see Clinical Studies (14.3)]*. The trials required an absolute neutrophil count ≥1 x 10^9/L, platelet count ≥50 or ≥75 x 10^9/L and adequate hepatic function and excluded patients requiring a strong CYP3A inhibitor or inducer. Patients received BRUKINSA 160 mg twice daily (97%) or 320 mg once daily (3%). The median age in both studies combined was 70 years (range: 37 to 95), 52% were male, 64% were Caucasian and 19% were Asian. Most patients (92%) had an ECOG performance status of 0 to 1. Eighty percent received BRUKINSA for 6 months or longer, and 67% received treatment for more than one year.

Two fatal adverse reactions (2.3%) occurred within 30 days of the last dose of BRUKINSA, including myocardial infarction and a Covid-19–related death.

Serious adverse reactions occurred in 40% of patients. The most frequent serious adverse reactions were pyrexia (8%) and pneumonia (7%).

Adverse reactions lead to treatment discontinuation in 6% of patients, dose reduction in 2.3%, and dose interruption in 34%. The leading cause of dose modification was respiratory tract infections (13%).

Table 7 summarizes selected adverse reactions in BGB-3111-214 and BGB-3111-AU-003.

Table 7: Adverse Reactions Occurring in ≥10% Patients with MZL Who Received BRUKINSA

Body System	Adverse Reaction	BRUKINSA (N=88)	
		All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection[a]	26	3.4
	Urinary tract infection[b]	11	2.3
	Pneumonia[c,d]	10	6
Gastrointestinal disorders	Diarrhea[e]	25	3.4
	Abdominal pain[f]	14	2.3
	Nausea	13	0
Skin and subcutaneous tissue disorders	Bruising[g]	24	0
	Rash[h]	21	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[i]	27	1.1
Vascular disorders	Hemorrhage[j]	23	1.1
General disorders	Fatigue[k]	21	2.3
Respiratory, thoracic and mediastinal disorders	Cough[l]	10	0

[a] Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, tonsillitis, rhinitis, viral upper respiratory tract infection.
[b] Urinary tract infection includes urinary tract infection, cystitis, Escherichia urinary tract infection, pyelonephritis, cystitis.
[c] Pneumonia includes COVID-19 pneumonia, pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection, organizing pneumonia.
[d] Includes 2 fatalities from COVID-19 pneumonia.
[e] Diarrhea includes diarrhea and diarrhea hemorrhagic.
[f] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort.
[g] Bruising includes contusion, ecchymosis, increased tendency to bruise, post procedural contusion.
[h] Rash includes rash, rash maculo-papular, rash pruritic, dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, drug reaction with eosinophilia and systemic symptoms, erythema, photosensitivity reaction, rash erythematous, rash papular, seborrheic dermatitis.
[i] Musculoskeletal pain includes back pain, arthralgia, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal chest pain, bone pain, musculoskeletal discomfort, neck pain.
[j] Hemorrhage includes epistaxis, hematuria, hemorrhoidal hemorrhage, hematoma, hemoptysis, conjunctival hemorrhage, diarrhea hemorrhagic, hemorrhage urinary tract, mouth hemorrhage, pulmonary hematoma, subcutaneous hematoma, gingival bleeding, melena, upper gastrointestinal hemorrhage.
[k] Fatigue includes fatigue, lethargy, asthenia.
[l] Cough includes cough and productive cough.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included peripheral neuropathy, second primary malignancies, dizziness, edema, headache, petechiae, purpura, and atrial fibrillation or flutter.

Table 8 summarizes select laboratory abnormalities.

Table 8: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with MZL

Laboratory Abnormality[a]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	43	15
Platelets decreased	33	10
Lymphocytes decreased	32	8
Hemoglobin decreased	26	6
Chemistry abnormalities		
Glucose increased	54	4.6
Creatinine increased	34	1.1
Phosphate decreased	27	2.3
Calcium decreased	23	0
ALT increased	22	1.1

[a] The denominator used to calculate the rate varied from 87 to 88 based on the number of patients with a baseline value and at least one post-treatment value.

Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The safety data described below reflect exposure to BRUKINSA (160 mg twice daily) in 675 patients with CLL from two randomized controlled clinical trials *[see Clinical Studies (14.4)]*. The trial required patients to be unsuitable for fludarabine, cyclophosphamide, and rituximab (FCR) therapy defined as age ≥65 years, or age 18 to <65 years with either a total Cumulative Illness Rating Scale (CIRS) >6, creatinine clearance 30 to 69 mL/min, or history of serious or frequent infections. The trial excluded patients with AST or ALT ≥2 times the upper limit of normal (ULN) or bilirubin ≥3 times (ULN) and patients requiring a strong CYP3A inhibitor or inducer.

SEQUOIA

The safety of BRUKINSA monotherapy in patients with previously untreated CLL/SLL was evaluated in a randomized, multicenter, open-label, actively controlled trial *[see Clinical Studies (14.4)]*. Patients without deletion of chromosome 17p13.1 (17p deletion) (Cohort 1) received either BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity (n=240) or bendamustine plus rituximab (BR) for 6 cycles (n=227). Bendamustine was dosed at 90 mg/m^2/day intravenously on the first 2 days of each cycle, and rituximab was dosed at 375 mg/m^2 on day 1 of Cycle 1 and 500 mg/m^2 on day 1 of Cycles 2 to 6.

Additionally, the same BRUKINSA regimen was evaluated in 111 patients with previously untreated CLL/SLL with 17p deletion in a non-randomized single arm (Cohort 2).

Randomized cohort: Previously untreated CLL/SLL without 17p deletion

In patients with previously untreated CLL/SLL without 17p deletion, the median age was 70, 62% were male, 89% were White, 2% were Asian, and 2% were Black. Most patients (93%) had an ECOG performance status of 0 to 1.

The median duration of exposure to BRUKINSA was 26 months, with 71% exposed for more than 2 years.

Serious adverse reactions occurred in 36% of patients who received BRUKINSA. Serious adverse reactions that occurred in ≥5% of patients were COVID-19, pneumonia, and second primary malignancy (5% each). Fatal adverse reactions occurred in 11 (4.6%) patients with the leading cause of death being COVID-19 (2.1%).

Adverse reactions led to permanent discontinuation of BRUKINSA in 8% of patients, dose reduction in 8%, and dose interruption in 46%. The most common adverse reactions leading to permanent discontinuation were second primary malignancy and COVID-19. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and hemorrhage.

Table 9 summarizes select adverse reactions in this randomized cohort.

Table 9: Adverse Reactions in ≥10% Patients with Previously Untreated CLL/SLL Without 17p Deletion in SEQUOIA

System Organ Class Preferred Term	CLL/SLL without 17p deletion			
	BRUKINSA (N=240)		BR (N=227)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a]	33	1.7	17	0.4
Infections and infestations				
Upper respiratory tract infection[b]	28	1.3	15	0.9
Pneumonia[c]	13*	5	8†	4
Vascular disorders				
Hemorrhage[d]	27*	4	4	0.4
Hypertension[e]	14	7	5	2.6
Skin and subcutaneous tissue disorders				
Rash[f]	24	1.3	30	5
Bruising[g]	24	0	2.6	0
Respiratory, thoracic and mediastinal disorders				
Cough[e]	15	0	10	0
Gastrointestinal disorders				
Diarrhea	14	0.8	12†	0.9
Constipation	10	0.4	18	0.0
Nausea	10	0	33	1.3
General disorders				
Fatigue[h]	14	1.3	21	1.8
Neoplasms				
Second primary malignancy[i]	13*	6	1.3	0.4
Nervous system disorders				
Headache[e]	12	0	8	0
Dizziness[j]	11	0.8	5	0

* Includes 3 fatal outcomes.
† Includes 2 fatal outcomes.
[a] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, musculoskeletal discomfort, bone pain.
[b] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, laryngitis, tonsillitis and upper respiratory tract inflammation, and related terms.
[c] Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.
[d] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[e] Includes multiple similar adverse reaction terms.
[f] Rash: Rash, dermatitis, drug eruption, and related terms.
[g] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[h] Fatigue: fatigue, asthenia, and lethargy
[i] Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including lung, renal, genitourinary, breast, ovarian, and rectal), and chronic myeloid leukemia.
[j] Dizziness: dizziness and vertigo.

Other clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included COVID-19 (9%), edema (8%), abdominal pain (8%), urinary tract infection (7%), and atrial fibrillation or flutter (3.3%).

Table 10 summarizes select laboratory abnormalities in this cohort.

Table 10: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL without 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA		BR	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	37	15	80	53
Hemoglobin decreased	29	2.5	66	8
Platelets decreased	27	1.7	61	11
Leukocytes increased	21[b]	21	0.4	0.4
Chemistry abnormalities				
Glucose increased[c]	55	7	67	10
Creatinine increased	22	0.8	18	0.4
Magnesium increased	22	0	14	0.4
Alanine aminotransferase increased	21	2.1	23	2.2

[a] The denominator used to calculate the rate was 239 in the BRUKINSA arm and 227 in the BR arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.
[b] Lymphocytes increased in 15%.
[c] Non-fasting conditions.

Single-arm cohort: Previously untreated CLL/SLL and 17p deletion

In 111 patients with previously untreated, 17p del CLL/SLL, the median age was 70, 71% were male, 95% were White, and 1% were Asian. Most patients (87%) had an ECOG performance status of 0 to 1. The median duration of exposure to BRUKINSA was 30 months.

Fatal adverse reactions occurred in 3 (2.7%) patients, including pneumonia, renal insufficiency, and aortic dissection (1 patient each).

Serious adverse reactions occurred in 41% of patients treated with BRUKINSA. Serious adverse reactions reported in ≥5% of patients were pneumonia (8%) and second primary malignancy (7%).

Adverse reactions led to treatment discontinuation in 5% of patients, dose reduction in 5%, and dose interruption in 51%. The leading causes of dose modification (≥5% of all patients) were pneumonia, neutropenia, second primary malignancy, and diarrhea.

Table 11 summarizes select adverse reactions in this cohort.

Table 11: Adverse Reactions in ≥10% of Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

System Organ Class Preferred Term	CLL/SLL with 17p Deletion	
	BRUKINSA (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations		
Upper respiratory tract infection[a]	38	0.0
Pneumonia[b]	20*	8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[c]	38	2.7
Skin and subcutaneous tissue disorders		
Rash[d]	28	0.0
Bruising[e]	26	0.9
Vascular disorders		
Hemorrhage[f]	28	4.5
Hypertension[g]	11	5.4
Neoplasms		
Second primary malignancy[h]	22†	6
Gastrointestinal disorders		
Diarrhea	18	0.9
Nausea	16	0.0
Constipation	15	0.0
Abdominal pain[g]	12	1.8
Respiratory, thoracic and mediastinal disorders		
Cough[g]	18	0.0
Dyspnea[g]	13	0.0
General disorders and administration site conditions		
Fatigue[i]	14	0.9
Nervous system disorders		
Headache	11	1.8

* Includes 1 fatal outcome.
† Includes non-melanoma skin cancer in 13%.
[a] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, upper respiratory tract inflammation, viral upper respiratory tract infection, and related terms.
[b] Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, and related terms including specific types of infection.
[c] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, bone pain.
[d] Rash: Rash, dermatitis, toxic skin eruption, and related terms.
[e] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[f] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[g] Includes multiple similar adverse reaction terms.
[h] Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including bladder, lung, renal, breast, prostate, ovarian, pelvis, and ureter), and malignant melanoma.
[i] Fatigue: fatigue, asthenia, and lethargy.

Clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included urinary tract infection (8%), edema (7%), atrial fibrillation or flutter (4.5%), and COVID-19 (3.6%).

Table 12 summarizes select laboratory abnormalities in this cohort.

Table 12: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	42	19[b]
Hemoglobin decreased	26	3.6
Platelets decreased	23	0.9
Chemistry abnormalities		
Glucose increased[c]	52	6
Magnesium increased	31	0
Creatinine increased	27	0.9

[a] The denominator used to calculate the rate varied from 110 to 111 based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.
[b] Grade 4, 9%.
[c] Non-fasting conditions.

ALPINE

The safety of BRUKINSA monotherapy was evaluated in patients with previously treated CLL/SLL in a randomized, multicenter, open-label, actively controlled trial *[see Clinical Studies (14.4)]*. In ALPINE, 324 patients received BRUKINSA monotherapy, 160 mg orally twice daily and 324 patients received ibrutinib monotherapy, 420 mg orally daily until disease progression or unacceptable toxicity.

In ALPINE, the median duration of exposure was 24 months for BRUKINSA. Adverse reactions leading to death in the BRUKINSA arm occurred in 24 (7%) patients. Adverse reactions leading to death that occurred in >1% of patients were pneumonia (2.8%) and COVID-19 infection (1.9%).

One hundred and four patients in the BRUKINSA arm (32%) reported ≥1 serious adverse reaction. Serious adverse reactions occurring in ≥5% of patients were pneumonia (10%), COVID-19 (7%), and second primary malignancies (5%).

Adverse reactions led to treatment discontinuation in 13% of patients, dose reduction in 11%, and dose interruption in 42%. The leading cause of treatment discontinuation was pneumonia. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and neutropenia.

Table 13 summarizes select adverse reactions in ALPINE.

Table 13: Adverse Reactions in ≥10% of Patients with Relapsed or Refractory CLL/SLL Who Received BRUKINSA in ALPINE

System Organ Class Preferred Term	BRUKINSA (N=324)		Ibrutinib (N=324)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				
Upper respiratory tract infection[a]	27	1.2	22	1.2
Pneumonia[b]	18*	9	19†	11
COVID-19[c]	14*	7	10†	4.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[d]	26	0.6	28	0.6
Vascular disorders				
Hemorrhage[e]	24*	2.5	26†	3.7
Hypertension[f]	19	13	20	13
Skin and subcutaneous tissue disorders				
Rash[g]	20	1.2	21	0.9
Bruising[h]	16	0.0	14	0.0
Gastrointestinal disorders				
Diarrhea	14	1.5	22	0.9
General disorders				
Fatigue[i]	13	0.9	14	0.9
Respiratory, thoracic and mediastinal disorders				
Cough[f]	11	0.3	11	0.0
Nervous system disorders				
Dizziness[i]	10	0.0	7	0.0

* Includes fatal outcomes: pneumonia (9 patients), COVID-19 (8 patients), and hemorrhage (1 patient).
† Includes fatal outcomes: pneumonia (10 patients), COVID-19 (9 patients), and hemorrhage (2 patients).
[a] Upper respiratory tract infection: upper respiratory tract infection, sinusitis, pharyngitis, rhinitis, nasopharyngitis, laryngitis, tonsillitis, and related terms.
[b] Pneumonia: Pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.
[c] COVID-19: COVID-19, COVID-19 pneumonia, post-acute COVID-19 syndrome, SARS-CoV-2 test positive.
[d] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, bone pain, and musculoskeletal discomfort.
[e] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[f] Includes multiple similar adverse reaction terms.
[g] Rash: Rash, Dermatitis, and related terms.
[h] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[i] Fatigue: asthenia, fatigue, lethargy.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included urinary tract infection (9%), supraventricular arrhythmias (9%) including atrial fibrillation or flutter (4.6%), abdominal pain (8%), headache (8%), pruritus (6.2%), constipation (5.9%), and edema (4.6%).

Table 14 summarizes select laboratory abnormalities in ALPINE.

Table 14: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients Who Received BRUKINSA in ALPINE

Laboratory Abnormality[a]	BRUKINSA		Ibrutinib	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	43	15	33	16
Hemoglobin decreased	28	4	32	3.7
Lymphocytes increased	24	19	26	19
Platelets decreased	22	4	24	3.4
Chemistry abnormalities				
Glucose increased	52	5	29	2.8
Creatinine increased	26	0.0	23	0.0
Phosphate decreased	21	2.5	13	2.2
Calcium decreased	21	0.6	29	0.0

[a] The denominator used to calculate the rate was 321 in the BRUKINSA arm, and varied from 320 to 321 in the ibrutinib arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 15: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when coadministered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid coadministration of BRUKINSA with strong CYP3A inducers *[see Dosage and Administration (2.3)]*. • Avoid coadministration of BRUKINSA with moderate CYP3A4 inducers *[see Dosage and Administration (2.3)]*. If these inducers cannot be avoided, increase BRUKINSA dosage to 320 mg twice daily *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures *(see Data)*. Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2 or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre and postnatal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g., cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for 1 week following the last dose of BRUKINSA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving BRUKINSA and for 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1550 patients with MCL, MZL, WM, and CLL/SLL in clinical studies with BRUKINSA, 61% were ≥65 years of age, and 22% were ≥75 years of age. Patients ≥65 years of age had numerically higher rates of Grade 3 or higher adverse reactions and serious adverse reactions (63% and 47%, respectively) than patients <65 years of age (57% and 36%, respectively). No overall differences in effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥15 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

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The Sensei Way

BY BRANDI BROWER

Sensei- a noun: a teacher or instructor usually of Japanese martial arts.

When I hear the word "Sensei," images are conjured in my mind of the 80's film, The Karate Kid. When the boy, Daniel, befriends an older man, his instructor, Mr. Miyagi, teaches him skills through work that will help him defend himself: "Wax on, right hand. Wax off, left hand. Breathe, in through the nose, out through the mouth. Wax on, wax off. Don't forget to breathe. Very important." I love this movie because the Sensei, Mr. Miyagi, gives sage wisdom and counsel that the young student can use throughout his life (and through several film sequels!) I will draw upon several "Miyagi-isms" to help outline my recent travel experience and Sensei journey.

Sensei Lana'i, A Four Seasons Resort, is an adults-only wellness enclave in the beautiful remote Hawaiian island of Lana'i. Reputable experts, extraordinary facilities, a breathtaking setting, and the infamous hospitality the lux brand is renowned for are a recipe for success. The Sensei Way philosophy focuses on three paths - move, nourish, and rest. Co-founders tech giant and billionaire Larry Ellison and best-selling author, scientist, and oncologist Dr. David Agus have created this zen habitat up against the hills of the Hawaiian island to offer a place to fuel your passions and connect with your intentions. Their wellness focus:

Movement is how we interact with our environment.
Nourishment is what fuels us.
Rest is how we recover.

Let the promise of greater wellness begin.

A questionnaire is sent to me electronically in preparation for my visit. My Sensei retreat will not be a traditional spa getaway for facials and massage treatments. The first clue was the questions asked about my wellness goals and what I hoped to accomplish during a follow-up call from a Sensei team member after seeing the results of my questionnaire. They are committed to the process of shepherding their sheep.

Mr. Miyagi: "Walk Left Side, Safe. Walk Right Side, Safe. Walk Middle, Sooner Or Later... Get Squish Just Like Grape!" When the teacher asked Daniel if he was ready to begin training, he

responded, "I guess so." He needed the life lesson of committing fully to something. Mr. Miyagi followed up the illustration with "...same with karate. You karate 'yes,' or you karate 'no.' You karate 'guess so,' squish just like grape. Understand?" I had to say 'yes' to my Sensei journey in Lana'i; no lukewarm attitude allowed, but a total commitment to wellness.

My plane touches down in Honolulu, and I am whisked away by a greeter and driven in a private car over to the reception area of an air terminal for Lana'i Air. I relaxed in the lovely appointed lounge with a view of Diamond Head, served tea and Hawaiian shortbread cookies while the private plane was being prepared. Another couple joined me on the golf cart that took us to the awaiting jet. A quick 20-minute flight and we are flying over the secluded island of Lana'i with just over 3000 residents—a stark contrast from Oahu, which has nearly one million. Upon landing, Four Seasons team members told us our luggage would be waiting in our rooms. The cute couple is on a babymoon and heading for the Four Seasons Resort Lana'i; I'm heading in the opposite direction and climbing into the waiting Model X Tesla with its winged doors for the last leg of my trip. We pass Lana'i City, a little town with small shops, grocery stores, eating spots, and a few stop signs but no street lights. At 1600 feet above sea level, the short drive from the airport gives an unexpected mountain vibe as I see more decades-old Cook Island Pines than palm trees. Sensei Lana'i greeters meet me with smiles, a ceremonial tea, and a welcoming Kukui nut lei placed around my neck.

Immediately, I was amazed by the immense beauty of the grounds, ardent landscape design, and elite, grand sculptures. I'm so enthralled with the magical property that my heart dips a bit, knowing I can't stay here forever. It's like a Garden of Eden, with lagoons, walking trails, and lush green curated spaces, but instead of the Biblical tree of knowledge of good and evil, a massive Banyan tree! It's no accident that Colombian artist Fernando Botero's Adam and Eve, which stand under the tall, slender pines, are holding an apple in their bulbous hands, a reminder that, like paradise, this special place is abundant in life. So much color and energy that you could wander for days and still find corners and secrets in this unique garden. All intentional, a master plan to help guests begin their healing through their connection with nature.

What was once the rustic style, Lodge at Koele, is a completely redesigned and reimagined oasis that rests in the Upcountry against Koloidi Ridge, an estimated $75 million renovation. The four-year project resulted in a gorgeous grand country estate with a wrap-around porch, rocking chairs, white shutters, and a glass-fronted great hall. Checking in was enjoyable as I was invited to one of the stylish furniture groupings for the process. The two striking anchors of the great room are the floor-to-ceiling massive fireplaces at either end. The elegant lobby, decorated in neutral shades of tan, cream, and white tones, with wood beams, stylish lighting, accented by orchids, and impressive art, is a light-filled and perfect space; it oozes with absolute attention to every design element and detail.

On the walk to my guest room, one of just over 100 at the resort, we pass dramatic 3D art installations, mirror-polished stainless steel "Aphrodite" by Jeff Koons, two giant cherries, and several other modern pieces, and that's just the length of distance to my suite. Like the great hall aesthetic, the room palette has airy neutrals and cozy and calming materials—Four Seasons lux standard-issue pillows, beds, sheets, and comforters. White shutter blinds above a cute cushioned window seat add charm along with the door out to the garden veranda. Great natural light, desk, large flat screen tv, in-room tablet, marble accents, Japanese bidet, and two-person shower are nice extras. As serene as the room is, I've got wellness goals, and I'm not planning on spending much time here other than sleeping.

My introduction to the Sensei Way began with My Intention. This hour-long session was with one of my instructors, my mindset guide, Lydia. We sit across each other in comfortable chairs; a wall of screens is in front of me to project information and data. She asks me many questions about myself, my work/life balance, and why I'm on this journey. Through the mindset discussion, she shares the focus of the three paths that will help me get familiar with and maintain a conversation with my body and mind. We discuss my wellness goals from my pre-arrival questionnaire and how they can help facilitate actionable steps. I was asked to step on a bioelectrical impedance analysis machine, which uses technology to calculate various measurements of my body mass and water. (I'm not particularly eager to get on any scales, so this was a leap of faith) Lydia asked me to do a series of movements to assess mobility and balance. *Miyagi-ism: "You Trust The Quality Of What You Know, Not Quantity." I was stepping out of my comfort zone and trusting in the "quality" of this process for my greater good.

I'm impressed with my carefully curated itinerary—three full days of specific activities and training sessions, especially for me. But the list of classes, treatments, and experiences is numerous. My schedule barely scratches the surface of health and wellness opportunities at the stunning sanctuary; spa treatments, off-site excursion options, exercise facilities, a library, and a 9000-square-foot saltwater pool are available if you can make the time.

I change into some workout clothes for my Fitness 1:1 with biomarkers meeting. Keri is my Sensei for fitness, a former athletic trainer to Olympiads; she brings a wealth of knowledge. She explains what we will be doing in this session. Through a maximal effort cardiovascular assessment (V02 max) on a treadmill, the practitioner will discover the efficiency of my heart while wearing a mask and hitting milestones on the treadmill. Using technology and analyzing the science of my cardiovascular system, I can improve my heart rate baseline and understand my maximum effort potential.

In the afternoon, I walked to one of the movement studios to learn the fundamentals of the ancient Chinese tradition of Tai Chi. I received training from the lovely instructor Akiko teaching me the art of patience and flow as I tried to perfect my "stroke the tail of the bird." It was exciting to find my chi and feel the internal energy. With a concentration on grace and balance, this exercise form is slow and focused, teaching you to move more confidently.



Now that I've got my flow back, I stroll over to the yoga pavilion and on the deck of the large pond for an open sky meditation. This 30-minute guided meditation uses touch, sound, and sight; the facilitator helps the small group focus on each of those senses to connect with the surrounding nature—a great way to expand awareness of the beauty and relax.

That evening I experienced Sensei by Nobu. Famed global gastronomy founder Nobu Matsuhisa brings the Nobu style cuisine to the island of Lana'i, describing it, "... the cooking is still Japanese but with some ingredients and styles from Peru like cilantro, jalapeno peppers, and ceviche." With fresh and natural ingredients, the guilt-free restaurant fits perfectly in with the Asian influences of the resort and the nutritional goals of the patrons. The large dining room gives the feeling of an atrium in the glass pavilion with floor-to-ceiling sliders that open up to feel the fresh night air and hear the soft sounds of the outdoors. It sits upon a lighted reflecting pond with numerous large koi fish. The Roasted Lobster Salad ignited my taste buds; Sensei Farm Tomatoes, Smoked Vinaigrette, Tropical Fruits, as well as the main course of Japanese Wagyu Beef; Sensei Farm Vegetables, Nobu Sauce Trio, and finishing with a Coffee Hazelnut Millefuille; Gianduja Feuilletine, Candied Hazelnuts, Bitter Chocolate Sorbet.

Up with the sun and feeling invigorated, I met the guide Mike for the Koloiki Ridge hike. A moderate level 4.9 mile climb up through the lush forest to the summit overlooking a panoramic view of Maui and Moloka'i. The Sensei Way distills preventative health science data and research into three simple paths: move, nourish, and rest. I moved up to the top of a mountain, Nobu nourished me, and now it was time to rest with my first hale treatment. There are ten luxurious hales, Japanese-inspired oases of calm, each building a substantial 1,000 square feet of pure indulgence. They feature an ofuro bathtub, infrared sauna, steam, indoor and outdoor showers, oversize massage tables, private plunge pools, and cozy lounging areas. After each spa experience, you get 30 to 60 minutes to soak up the self-care amenities in the private, peaceful little houses—my spa experience is an exclusive Sensei-developed thermal body mapping technology and massage. My practitioner Fran operated the machine to scan my body. She showed me the results on the tablet, which revealed inflamed tissues that I didn't even know were in distress. A visual map of my body showed her asymmetries, muscle tightness, and possible areas of pain. She used the data to target those specific areas to customize my massage to release tension and improve circulation. You know it's an incredible 90-minute experience when you hug the masseuse after.

I'm concerned that I will undo all the great work Fran accomplished in my trouble areas during my aerial yoga class. I had never done a class like this before. But I embraced the journey and stripped my inhibitions while stretching my body, thanks to my Sensei Ariel. With swaths of silk hanging from the secured beams in the yoga pavilion, I'm led through a series of movements that improve flexibility, stability, and balance. After the savasana, I felt the physical and psychological benefits of the practice and vowed to find an aerial yoga class when I returned home.

My last morning starts with Mindset 1:1 with Biomarkers. I meet again with my Sensei Lydia, who teaches the science of heart rate variability (HRV) and how to measure and influence my personal HRV through focused breathwork and guided imagery. *Miagy-ism: "When You Feel Life Out Of Focus, Always Return To Basic Of Life." (Breathing) Scientific studies have shown how breathing affects a person's stress level. People can overcome stressful situations by calming the mind, focusing, and taking deep breaths while reducing blood pressure, hypertension, and other ailments.

Lydia shared, "Resonance frequency is when the mind and body (breathing rhythms and heart rhythms) become synchronized. In stress and anxiety, there is no such rhythm - no input from the parasympathetic (rest/digest) branch of the nervous system. When you access this frequency through various tools, you train your nervous system, allowing you to be more focused, present, cognitively agile, and emotionally resilient."

Terry is my Sensei for a Functional Fascia class. Fascia is the connective tissue that surrounds muscles and organs, which until recent years has been ignored until new insights suggest it holds the key to tackling chronic pain and immune dysfunction. I'm guided through this private session, using various foam rolling tools and techniques to mobilize tissue, enhance somatic awareness, and explore recovery modalities for the whole body.

My favorite Sensei experience was the Aquatic Bodywork with my practitioner Liran. Watsu comes from the words "water" and "shiatsu," a Japanese word for finger pressure. While floating effortlessly in the perfect 96-degree warm water of the private outdoor hale pool, my therapist continuously supported and guided me through intuitive stretches combining massage, joint mobilization, and shiatsu elements.
The health advantages; include decreased physical pain, increased range of motion, improved healing and immune system response, and increased muscle relaxation and sleep patterns. The focus is on the physical benefits; however, there is a residual gift from this aquatic therapy, a profoundly emotional experience for some. People who have tried the Watsu therapy have likened it to a full mind, body, and spirit experience. It's a safe, womb-like environment where you are cradled like a child; in other moments, your body is free-flowing, and the water carries anxiety and stresses away. Some achieve higher awareness and fall into a deeply meditative state. After it was over, I told my practitioner that if everyone in the world could have this opportunity, I think it would be a better place. It was such a healing experience.

The Sensei journey ended with the My Plan session, a time to reflect on my experience at Sensei and collaborate with my guide Lydia to plan my most immediate and actionable next steps. Together we discussed my data metrics, expert analysis, and personal experiences to build my Guide to Growth. We discussed all that I learned during my time, my goals before my arrival, and how to take the knowledge I received back to the mainland and use it to achieve my goals. As we parted, Lydia shared, "Remember, all that you felt and discovered while here was created by you. It was in you before you arrived and is still in you after you have departed. We only guided." *Miagy-ism: "If Come From Inside You, Always Right One." Like Daniel's Sensei, Mr. Miagy, my guides taught me different skills through work that will help defend my body against imminent decay and offered sage counsel backed by science to help me throughout my life.



On my last night, I visited the onsen garden, a beautifully landscaped labyrinth of burbling streams, bridges, and footpaths with ten discreetly located private hot tubs sunk in the ground. With zero light pollution on the island, the stars were breathtaking as I relaxed in the warm water and felt like I was the only person on the planet. I reflected on my time at this special place, the lessons learned, my health plans, and what I wanted moving forward. I felt uniquely centered.

Kupuna Irene Kamāhuialanai Cockett Perry wrote this poem:

Mele hoʻokipa no kōʻele
I waena o ka Pākīpika, aia o Hawaiʻi.
I wanna o Hawaiʻi, aia o Lānaʻi.
Aia i ka mole o Lānaʻi, o kōʻele.
E hoʻokipa mai i kōʻele!

In the middle of the Pacific is Hawaiʻi.
In the center of Hawaiʻi is Lānaʻi.
At the heart of Lānaʻi is kōʻele.
Welcome to kōʻele!

Unsurprisingly, I have become more centered after my precious time at this remarkable place. This Four Seasons Resort is at the heart of Lanaʻi; this extraordinary Sensei retreat, this unique island, welcomed me, and I will be forever grateful for the gifts that were given.



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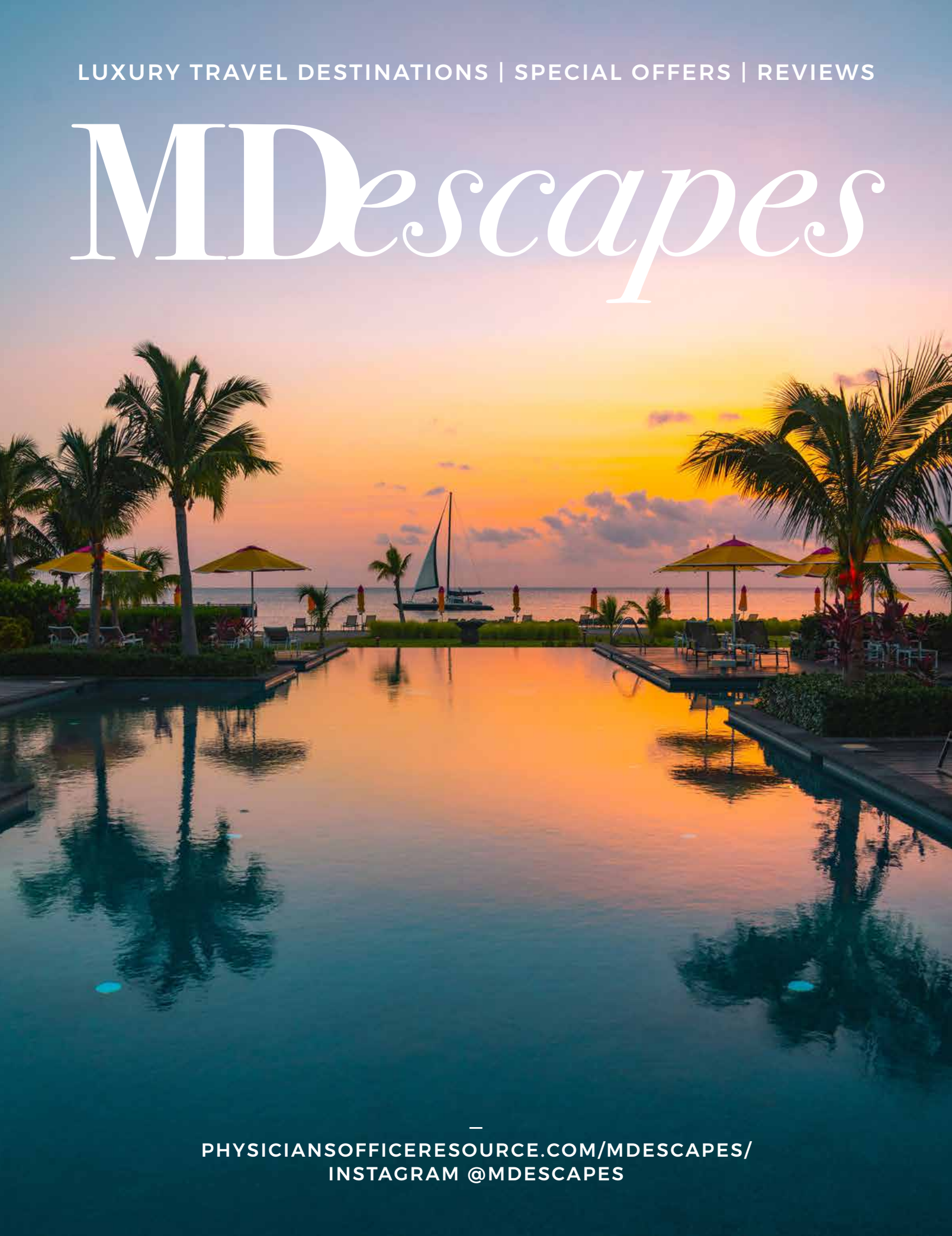
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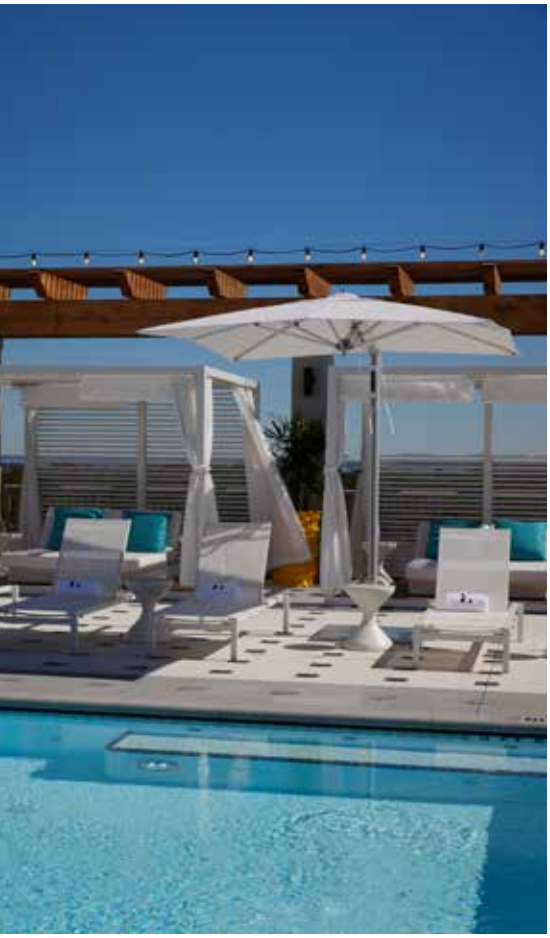
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[1] Brown, H. *Improving the Diagnosis of Vulvovaginitis.* Population Health Management. Vol. 23, suppl 1, 2020

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